OMB No. 0990-0115

Electronic Request for Proposal

SECTION A – SOLICITATION/CONTRACT FORM

OFFERORS ARE RESPONSIBLE FOR ROUTINELY CHECKING THE CMB WEBSITE http://www.niaid.nih.gov/contract/default.htm FOR ANY POSSIBLE SOLICITATION AMENDMENTS THAT MAY BE ISSUED. NO ADDITIONAL NOTIFICATION OF ANY AMENDMENTS WILL BE PROVIDED BY THIS OFFICE.

Purchase Authority: Public Law 92-218, as amended.
NOTE: The issuance of this solicitation does not commit the government to an award.

RFP Number:	***Just In Time:***	Small Bus. Set-Aside [ ]Yes [X]No 8(a) Set-Aside [ ]Yes [X]No NAICS Code: 54171 Size Standard: 500 Employees	***Level of Effort:*** [ ] Yes [X] No ***Total Effort:*** [ ]
NIH-NIAID-DMID-03-08	[ ] Yes [X] No		

TITLE: Clinical Trials for Antiviral Therapies

Issue Date: September 4, 2002	***Due Date: November 15, 2002*** ***Time:* 4:00 PM, EST**	***Technical Proposal Page Limits:*** [X] Yes *(see "How to Prepare and Submit Electronic Proposals")* [ ] No

ISSUED BY:
Lawrence M. Butler
Contracting Officer
Contract Management Branch, DEA
NIH, NIAID
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Room 2230, MSC 7612
Bethesda, MD 20892-7612

[X] We reserve the right to make awards without discussion.

NO. OF AWARDS:	***PERIOD OF PERFORMANCE:***
[X] Only 1 Award [ ] Multiple Awards	7 years beginning on or about 07/01/2003

Offers will be valid for 120 days unless a different period is specified by the Offeror on the form entitled "Proposal Summary and Data Record, NIH-2043" (See SECTION J - Attachments)

The Official Point of Receipt for the purpose of determining timely delivery is the Contract Management Branch as stated above. The paper copy with original signatures is the official copy for recording timely receipt. If the paper copy of your proposal is not received by the Contracting Officer or Designee at the place and time specified, then it will be considered late and handled in accordance with HHSAR 352.215-70 entitled "Late Proposals and Revisions" located in this Solicitation. FACSIMILE SUBMISSION OF PROPOSALS IS NOT ACCEPTABLE.

POINT OF CONTACT* -- Sharon Kraft *--COLLECT CALLS WILL NOT BE ACCEPTED--

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TABLE OF CONTENTS

Background

Clinical Trials for Antiviral Therapies
DMID-03-08

INTRODUCTION

This RFP solicits proposals for the re-competition of a contract for the coordination and conduct of clinical trials for antiviral therapies. The development of therapies for acute and chronic, non HIV, vial diseases is a programmatic priority of the Division of Microbiology and Infectious Diseases (DMID) of the National Institute of Allergy and Infectious Diseases (NIAID).

Under the current (ongoing) contract, studies are conducted for the evaluation of experimental therapies for severe viral infections, including but not limited to severe infections with herpesviruses, hepatitis viruses, respiratory syncitia virus, influenza virus, and hantavirus. In this proposed new award, the contract primarily will facilitate advances in clinical antiviral therapy by rigorously evaluating the safety, tolerability, dose selection and/or efficacy of new therapeutic regimens for herpesvirus infections. Studies to identify natural history of herpesvirus infections, to identify/quantitate surrogate markers of therapeutic activity for anti-herpesvirus therapies, and to document the development of resistance to these antiviral therapies will also be conducted. In addition, similar studies may be undertaken to evaluate the natural history of, and/or therapies for, other emerging or rare viral diseases and rare or severe viral infections in special populations of patients (e.g., immunocompromised, pediatrics, elderly, pregnant women), as directed by DMID and where there is an identified public health need that is not being adequately addressed by commercial endeavors. Finally, this program will also assess the safety, tolerability, and clinical pharmacology of promising antiviral therapeutics under development to counter emerging viral diseases or biologic threat agents (Bio-defense), as directed by the Project Officer (PO). To achieve these objectives, the Contractor shall establish, coordinate, and manage a collaborative clinical network hereafter referred to as the Collaborative Antiviral Study Group (CASG) to perform multiple clinical trials of therapies for these viral diseases and other studies outlined above.

The Contractor shall provide a Central Unit to provide clinical leadership and to support CASG activities. The Contractor shall provide operations, regulatory, statistical and data management and analysis functions in support of the CASG. The Contractor shall identify and enlist services of collaborating medical institutions to become part of the CASG and to perform these clinical trials. The Contractor shall be responsible for all administrative activities including, but not limited to, protocol development and administration, development of procedures to assess regulatory compliance of all clinical sites, clinical site monitoring to assure compliance with good clinical practices and adherence to the protocol, data collection and analysis. The Contractor shall provide biostatistical support for trial design, data management and analysis and a central laboratory for the coordination of patient specimen collection, processing, and testing. The Contractor shall coordinate protocol design and development for multiple studies and shall provide administrative support for protocol development, documentation of regulatory compliance and clinical monitoring. These trials will usually, but not necessarily, be conducted under Investigational New Drug Applications (IND) held by DMID/ NIAID. The Contractor shall provide DMID with all information requested by DMID for IND filings, provide for clinical site monitoring , and report serious adverse events in accordance with federal regulations and guidelines. Safety Monitoring Committees (SMCs), Independent Safety Monitors (ISM) or Data and Safety Monitoring Boards (DSMBs) will be established for each study as determined by DMID. The Committees will monitor ongoing trials designated by the DMID/NIAID Project Officer (PO). The Contractor shall arrange for an unblinded statistician to prepare monthly (or more frequent if necessary) safety reports on patients enrolled in the studies for the SMCs and DMSBs and the PO. DMID's Guidelines for ISMs, SMCs and DSMBs are provided as an attachment. Each of the requirements outlined above is further delineated in the Statement of Work.

Proposals should address all parts of the statement of work. The Government recognizes that a single Offeror may not have all of the expertise outlined above, but may sub-contract for services or expertise as needed, with the exception of expertise in the conduct of multi-center trials for antiviral therapies.

Viral diseases (other than HIV) account for significant morbidity and mortality as well as economic loss in the U.S. The impact of viral infections is even more devastating worldwide. Although many of the disease syndromes caused by viruses are relatively benign and self-limited in the normal host, they are often much more severe in the immunocompromised, elderly, or pediatric populations. Many of these infections are "rare" and can only be studied

as a collaborative effort. Clinical trials of new therapies for rare viral diseases or viral diseases in special populations remain underserved by the international pharmaceutical industry due to the lack of adequate market potential.

Natural history studies (with or without evaluation of therapies) of rare or emerging viral diseases, particularly in special patient populations such as the immune compromised, provide critical data on the clinical disease progression for the design of future therapeutic trials. In addition, assessment of the impact of the development of resistance to important antiviral products is an important public health issue.

It has become apparent that several viruses may be used as agents of bioterrorism. Development of potential therapies against these agents is a new programmatic priority of DMID/NIAID. The lack of a potential market, as well as the difficulties associated with clinical testing of products for a clinical syndrome that may not occur naturally, make it difficult for a pharmaceutical company to justify the investment in development of these products. Thus, clinical studies to evaluate safety, tolerability and pharmacokinetics/ pharmacodynamics of promising new therapeutics are a critical component of a comprehensive US government Bio-defense plan.

In general, treatment of non-HIV viral infections and establishment of the natural history of rare or emerging viral diseases are high priorities of NIAID. Clinical trials for antiviral therapies have been an integral part of a comprehensive NIAID antiviral research program since1969. A program to evaluate promising antiviral therapies for severe herpesvirus diseases was begun in 1972 with an award to the University of Alabama at Birmingham (UAB). In 1996, the program was expanded to include clinical studies of other rare viral diseases as a result of an independent scientific review process. Trials often incorporated studies on the natural history and pathogenesis of viral diseases as preludes to the design of therapeutic studies. Studies undertaken routinely evaluated the use of contemporary laboratory methodology in the diagnosis, medical management and establishment of therapeutic outcome.

Historically, the contract has been performed under the auspices of the NIAID Collaborative Antiviral Study Group (CASG), a clinical network that presently consists of more than one hundred clinical investigators throughout the U.S., in addition to sites in Canada, England and Sweden. As the Central Unit of the CASG, the UAB coordinated and managed the performance of multiple clinical trials in immunocompetent and immunocompromised adult and pediatric populations. A central laboratory has been an integral part of this network and assisted in the development of critical diagnostic and outcome measures. The Central Unit also provided data management and biostatistical support. During the successive contract periods, the CASG has undertaken and completed numerous clinical trials that have identified therapeutic options for several rare infections of newborns and adults. Recently the CASG was utilized as part of the U.S. Bio-defense preparedness to provide a mechanism to implement a protocol to treat outbreaks of smallpox in the event of a release of the virus.

The CASG contract was recently (2001) reviewed by an independent panel of scientists. The following recommendations were made and have been incorporated into the statement of work for this RFP. New studies should focus primarily on antiviral therapies for herpesvirus infections. Other studies should be developed to evaluate strategies (e.g., surrogate markers, natural history/pathogenesis, antiviral drug resistance) to help evaluate future antiviral therapies. Finally the contract should include mechanisms to allow DMID to address future research needs and opportunities (e.g., other viral pathogens) as they arise. Since the review was completed, NIAID has embarked on a strategic Bio-defense plan of research on therapies for virus infections that are potential agents of bioterrorism. DMID decided to include capacity for early phase I/II testing of new therapies against these agents in the CASG contract.

Statement of Work
Clinical Trials for Antiviral Therapies
RFP-DMID 03-08

The Contractor shall, independently and not as an agent of the Government, furnish all necessary services, qualified personnel, materials, equipment and facilities not otherwise provided by the Government under the terms of this contract, as needed to perform the work set forth below.

SEE GENERAL NOTES TO OFFEROR: A-F

A. Clinical Leadership and Study Development

1. Provide clinical leadership (for adult and pediatric studies), scientific and medical advice and judgment regarding research options, for the development and implementation of protocols conducted under this contract.

2. Within 90 days of initiation of this contract, and yearly thereafter, the Contractor shall, in consultation and conjunction with the PO and NIAID staff, convene an ad hoc group of leading experts (including, but not limited to, infectious disease experts), that shall report directly DMID, to identify important potential studies relevant to the development of optimal therapies for herpesvirus infections and other medically significant, non-HIV, viral infections in special populations. The panel of experts shall:

    a) identify and address critical gaps in the existing knowledge of therapeutic status and discuss the types of studies described in this proposal that will address some of these gaps.
    b) review progress made on planning and implementing studies to address the identified gaps after the first year.
    c) shall identify required resources and address feasibility issues based on target enrollment projections.

    The panel will be convened annually to discuss new directions and to identify and recommend solutions to encountered problems. The Contractor shall provide funding for all costs incurred to convene the group of experts. In response to the recommendations from the panel, the Contractor shall develop a plan to delineate the mechanism by which new studies will be developed and prioritized. The plan will also address the mechanism for any re-prioritization of studies based on resources or in response to NIAID-directed studies for Bio-defense. The plan shall be updated annually, following the panel meeting, and submitted for review and approval by the PO. Public health needs and scientific opportunities may arise which will require revision of the research agenda before the annual submission. Any revisions must be submitted to the PO for review and approval prior to implementation.

SEE NOTES TO OFFEROR G-K

3. At the direction of the PO, develop and conduct rigorously designed single-center and multi-center controlled clinical trials to evaluate the safety and efficacy of therapies for herpesvirus infections and other serious non-HIV viral diseases in special populations (as recommended by the expert panel or NIAID).

4. At the direction of the PO, develop and conduct strategic, non-therapeutic, studies to support future therapeutic or medical management studies of herpesvirus infections or other medically important, rare viral diseases in special populations (as recommended by the expert panel or NIAID). These studies may include, but are not limited to, natural history/pathogenesis studies including immunologic responses of patients to infections, determination of resistance to antiviral therapies, development/testing of rapid viral diagnostic tests where these are needed, and identification of prognosticators/surrogate markers for outcome of therapy.

5. Provide clinical pharmacology expertise for the development and analysis of pharmacokinetic (exposure) studies and pharmacodynamic (exposure-response) studies for adult and pediatric populations.

SEE NOTE TO OFFEROR L

6. Develop and conduct, safety, exposure and/or exposure-response studies to support the development of therapeutics for emerging viral diseases and Bio-defense, as directed by the DMID PO.

7. To conduct the studies outlined in sections A 3-6 above, the Contractor shall establish, coordinate, and manage a collaborative clinical trials group (CASG). The Contractor shall:

    a) establish a Central Unit to support CASG activities.

    b) coordinate protocol design and development for all CASG studies.

    c) identify and enlist services of sufficient numbers collaborating medical investigators required to perform the clinical studies selected each year. Collaborating sites shall have a demonstrated access to patient populations defined by each protocol and the ability to enroll patients and to perform screening, entry and follow-up of patients as outlined in the protocols. Each site shall have an identified site-specific Principal Investigator with experience in clinical research involving evaluation of antiviral agents and the ability to comply with all protocol specifications and regulatory requirements.

    d) establish a plan for incentives and appropriate clinical study cost reimbursements for collaborating sites to participate in CASG studies. All incentive plans, which may be protocol specific, shall be submitted for review by the NIAID PO as they are developed, but shall be submitted annually at a minimum.

    e) develop a plan for soliciting, reviewing and prioritizing concepts for new clinical studies. The plan shall identify methods for determination of the relative merit of the proposed studies and methods for prioritizing based on resources, medical need, scientific merit, feasibility, and other criteria as needed. The plan should be submitted annually to the NIAID PO for review and approval. Concepts should address recommendations made by the panel of experts as outlined in section A-2.

    f) develop complete protocols for each clinical study. Protocols shall be reviewed and approved by the PO, NIAID, FDA, and the cognizant Institutional Review Boards (IRBs) prior to initiation of the clinical studies. Prepare or participate in the preparation of responses to FDA questions concerning submitted protocols.

    g) provide an infrastructure to ensure the proper conduct of clinical trials of antiviral therapies. The Contractor shall assume responsibility for the detailed planning, conduct, monitoring and reporting of clinical trials and associated studies.

8. Recruit and retain patients to ensure completion of protocols. Protocols should be completely enrolled in less than 5 years for each study. The Contractor shall ensure that minorities and both genders shall be included in clinical trials to comply with the current federal guidelines published in the Federal Register, Vol. 59, No. 59, March 28, 1994, which is provided as an attachment.

9. Serve as coordinator for the conduct of clinical trials that may be conducted in collaboration with non-NIAID clinical trials organizations. All collaborative efforts and procedures shall be reviewed for approval by the PO. All collaborators shall agree to follow procedures for the conduct of clinical trials that are acceptable to NIAID.

10. Identify strategies that may be implemented as part of some of the clinical studies that encourage professional development of new clinical scientists in the field of clinical trials for antiviral therapies..

11. Prepare a list of responsibilities(LOR) delineating the role of the CASG Central Unit, CASG collaborating investigators, pharmaceutical industry collaborators (if any), in the implementation of each study undertaken. The LOR shall identify key personnel for each role for each study. The LOR shall be submitted to the NIAID PO for review and approval at least 60 days prior to initiation of the study.

12. Organize and maintain protocol teams for each study in collaboration with the CASG collaborating investigators, pharmaceutical industry collaborators and NIAID. Each protocol team shall be led by a protocol chair and will be responsible for the development of the study protocol and case report forms, overseeing implementation of the protocol at participating sites, monitoring study progress, addressing study issues as they arise, and preparing and submitting manuscripts for publication in a timely manner. Whenever possible and practical, the Contractor shall encourage the selection and nurturing of junior investigators as part of the protocol team. Coordinate protocol development meetings for the writing of study protocols.

13. Coordinate the preparation of all reports, manuscripts and presentations involving data from group studies. Establish a publication policy for results of multicenter studies. All publications shall acknowledge NIAID support. The PO shall have access to all data generated and provide clearance for publication/disclosure of these data in manuscripts, abstracts, and presentations.

14. Develop and implement a policy and related procedures for the divulgence of real and potential conflicts of interest (COI) on the part of the investigators participating in the studies supported by this contract. The policy must be acceptable to NIAID and compatible with FDA regulations on financial disclosure by clinical investigators. The policy must address any COI that may occur through financial interest or other associations between CASG membership (including all participating investigators) and the private sector.

15. Organize and conduct an annual CASG investigators' Meeting in the Washington, DC area. The annual CASG Investigators' meeting shall include presentation and review of data, updates on the progress of all studies, discussion of proposed protocols, and the groups' standard procedures and active solicitation of ideas from the investigators for new concepts and research priorities for each research subcommittee to update the proposed overall group scientific agenda. Meetings and/or conference calls of individual protocol subcommittees shall be organized and conducted as needed. The Contractor shall provide funding for at least one investigator from each CASG site to attend this meeting. The Contractor shall provide funding for all costs incurred to conduct these meetings.

16. Prepare a transition plan for transfer of the data and data systems to a successor contractor if other than the incumbent, or as specified, upon 90 days notice by the PO.

B. Statistical Leadership, Data Management and Systems Development and Data Analysis and Reporting

1. Provide statistical leadership, scientific advice and judgment regarding clinical study design options, for the development and implementation of protocols conducted under this contract. Provide statistical expertise for other projects such as other NIAID-DSMB groups as requested by the PO.

SEE NOTE TO OFFEROR M

2. As part of the protocol development team, the statistical staff will collaborate with CASG investigators and NIAID staff to develop and refine other aspects of the experimental design of clinical studies, that may include, but is not limited to:

    a) Delineation of the research question to be addressed.
    b) Consultation on concepts to be developed by the CASG study groups or other investigators.
    c) Selection of appropriate study populations and control or comparison groups.
    d) Development of inclusion and exclusion criteria.
    e) Definition of clinical endpoints and surrogate markers.
    f) Selection of randomization and stratification/blocking methods.
    g) Development of data collection forms.
    h) Development of interim and final analysis methods.
    i) Development and implementation of quality assurance methods.
    j) Development of recommendations for modifications in the design of ongoing. clinical trials with respect to the above parameters, as determined by the Project Officer.
    k) Development of the case report forms.

3. Develop innovative approaches, as needed, for analyzing outcome data, including development of improved criteria for evaluating disease stages in conjunction with CASG investigators, and development of new statistical methods or modification of existing methods for data analysis that will better address relevant clinical research questions.

4. Establish and administer efficient, reliable, secure, and responsive systems for the collection, management, quality assurance, analysis and reporting of study data, as well as a system for communication linkages (preferably electronic) among CASG sites, the NIAID, the Central Unit, protocol teams and the expert panel, as needed.

5. Develop computer programs and related procedures for the collection, processing, editing, and analysis of all clinical and laboratory study data, including storage, tracking, and retrieval of study data at the central data management facility.

6. Produce and distribute standardized forms for the collection of all data needed on study subjects, including eligibility, demographic and other baseline data, sequential clinical outcome assessments, serious adverse events and side effects, and laboratory results. Work with the CASG investigators and the NIAID in the development and pre-testing of forms and procedures; reproduce and distribute all forms and revise as directed by the Project Officer.

7. Provide centralized computerized registration, randomization, and stratification of all patients on CASG protocols, or alternative non-computerized methods as directed by the Project Officer, including built-in checks for breakdowns in the assignment process, and procedures for monitoring masking of randomized treatment assignment codes.

8. Collect study data from participating CASG study sites. Using computerized data management systems developed in response to B 5 above, verify, process, monitor, correct, update, file and store the data securely and in accordance with applicable FDA regulations. Contact study personnel to obtain clarifications or corrections for questionable data or to correct deficiencies.

9. Develop and implement quality assurance and quality control procedures to detect data deficiencies.

10. Evaluate and improve the accuracy, timeliness and completeness of data submitted by the CASG clinical sites at each stage through the creation of final datasets, including verification of the clinical and laboratory data used to determine that study participants meet inclusion/exclusion criteria and/or have reach protocol-defined endpoints.

11. Develop and implement a system for evaluating protocol adherence by the CASG clinical sites and performance and quality of the data from the Central Laboratory.

12. Design and conduct interim and final statistical analyses of study data as directed by the PO and in collaboration with the CASG clinical leadership, the study Principal Investigator, NIAID staff and industry partners (if any) including but not limited to :

    a) conducting comprehensive statistical analyses, including relevant subgroup and exploratory analyses.
    b) preparing interim analyses of data on the safety, toxicity, and efficacy of interventions evaluated in studies for presentation to and review by the DSMBs, SMBs, and the NIAID. The analyses may also include analyses of data on accrual, retention, loss to follow-up and other status indicators relevant to the conduct of the studies.
    c) responding to requests for additional analyses from the CASG, DSMBs, SMCs, IRBs and NIAID. These analyses will be conducted only as needed to evaluate the safety and efficacy of therapeutic interventions. (For budget projections, it is estimated that at most one-two additional analyses will be required in any given year of this contract.)

13. Prepare study status and site-specific performance reports including, but not limited to, accrual and retention of study participants, timeliness of data submission, and adherence to protocol specifications, at least quarterly, for CASG studies for review by the appropriate CASG clinical site coordinator, the

appropriate DSBM or SMC and the NIAID with recommendations for improvements and modifications to resolve study issues and problems. Provide monthly (or more frequent if necessary) safety reports on patients enrolled in studies for the SMCs, DSMBs and the DMID person designated by the PO as the DSMB coordinator. (These reports shall be prepared by an statistician who is unblinded to the study under report.)

14. Prepare reports based on interim analyses data on the safety, toxicity, and efficacy of interventions evaluated in studies for presentation to and review by DSMBs, SMCs, and the NIAID.

15. Prepare annual and final IND study reports for clinical trials conducted under IND in this contract.

16. Participate in the preparation of scientific manuscripts and reports of the studies for publication in the peer-reviewed literature and presentation of the study results at relevant scientific meetings in collaboration with protocol chairs, other CASG investigators, NIAID, and others, as appropriate.

C. Central Laboratory

SEE NOTE TO OFFEROR N

1. Develop virologic assay methodology appropriate to assess outcomes in clinical trials. Prepare standard operating procedures for assay conduct and sample collection and handling. The Contractor will characterize each assay for overall performance in accordance with suggested guidelines issued by the U.S. Food and Drug Administration and will provide reports and data about the performance characteristics for each assay as requested by the Project Officer.

2. Package, inventory, ship and track patient specimens to the appropriate site as directed by the Project Officer or as outlined in the protocol. Prepare standard operating procedures for notification of shipment and verification of shipment receipt including, but not limited to, condition of specimens on arrival.

3. Provide leadership in the design of laboratory studies for basic biochemical, virologic and immunologic studies, including assays to assess viral load, antiviral drug resistance or to assist in medical diagnosis or medical management of patients. Prepare standard operating procedures for conduct of assays and sample collection and handling.

4. Develop protocols for the storage and use by other investigators of any clinical samples deemed necessary and allowable under current federal guidelines.

5. Develop and implement an inventory system to track specimens and consent of subjects/patients for future use of specimens.

D. Operations and Support

1. Provide operations and administrative support to the CASG and the NIAID for the conduct of clinical trials including, but not limited to the following:

    a. coordinate and assist with the protocol development process in collaboration with the designated protocol chair and team. Teams may include the protocol chair, principal investigator, NIAID representatives, industrial partners (if any), biostatistical expert, clinical trials specialist , data manager, and other investigators and specialists (as needed). Develop and prepare draft and final protocols with related documents, including informed consent and case report forms.

SEE NOTE TO OFFEROR O

    b. provide a repository for current versions of protocols, informed consent documents, case report forms, and other documents. Prepare summary minutes of all conference calls and protocol development meetings. Distribute copies to study sites, NIAID staff and others upon request by the NIAID PO.

c. prepare and update, as directed by the NIAID PO, a Manual of Procedures for each clinical protocol delineating specific instructions, requirements and guidelines for the conduct of clinical trials by the clinical sites, including, but not limited to, procedures for the collection, testing storage, and shipping of patient samples; instructions regarding the study laboratory procedures, specimen collection and preparation for shipping/transport; and any procedures for data collection, entry, verification, and storage as directed by the statistical staff or the NIAID PO.

d. design, produce and distribute labels for study materials, test articles, specimen containers, or data collections forms as required by study protocols.

e. prepare and distribute instructional materials regarding the study procedures and use these to conduct standardized training for study investigators and staff and clinical monitors using the Manual of Procedures and other materials. .

f. package, inventory, ship and track study test articles to sites.

g. organize protocol development, status review and start-up meetings/sessions as directed by the PO.

h. develop and maintain a tracking system (including expected timelines) for implementation and completion of studies.

i. enter and maintain the current status of CASG studies in DMID's required databases as directed by the PO.

j. provide DMID will all information requested by the DMID PO for IND filings. (Examples include IND-ready protocols; signed FDA-required investigator forms and copies of IRB approval letters.)

2. Ensure regulatory compliance of the clinical trials network

a. assist in assuring that all clinical trial sites are in compliance with all Federal regulations that apply to the conduct of research involving human subjects, including, but not limited to, Title 21 CRF 11, 50, 56 and 312 and Title 45 CFR 46.

b. provide technical and administrative assistance in the preparation of original and subsequent IND submissions including interim and annual reports. For all multi-center studies, review consent forms from all sites and ensure consistency with primary site consent form.

c. develop and maintain a computerized clinical site registration system including, but not limited to:

1) assembling and tracking initial and subsequent modifications of registration documentation submitted by clinical sites participating in the CASG clinical trials, including copies of the FDA form 1572, Curriculum Vitae, conflict of interest disclosure, IRB approval and annual reviews for each protocol, protocol amendment, consent form, and study advertisements.

2) assuring adherence to the informed consent forms submitted by each site to the NIAID approved informed consent template for each study.

3) confirming satisfactory completion of all procedures necessary for site registration to the Office of Regulatory Affairs (ORA) and the Project Officer and notifying clinical sites of study product shipment and enrollment study participants.

4) providing site registration status reports to NIAID and the CASG leadership.

5) confirming OHRP project assurance for each clinical site. No non-US sites may participate in a CASG study until documentation of compliance with these regulations has been submitted and prospectively approved by the Project Officer.

6) maintain site-specific regulatory files for each study.

d. establish and maintain a system for the receipt, follow-up, tracking, and disposition of serious adverse events (SAE) reports for all CASG clinical trials. The definition of an SAE will be included in each protocol and will be in accordance with FDA reporting rules.

e. satisfy FDA regulations and NIAID guidelines as related to processing of SAE reports and safety information by the following:

1) developing and distributing to participating clinical sites SAE reporting forms, standard operating procedures for processing adverse event data, and appropriate instructions or manuals. The forms shall be developed in coordination with CASG investigators and NIAID and shall conform to FDA regulations and NIAID guidelines.

2) establishing and maintaining a system for receiving faxes of SAE reports and related safety information 24 hours/day, 7 days a week.

3) abstracting and entering SAE data into the CASG database within 72 hours of receipt.

4) preparing draft safety reports for submission to NIAID that follow the established FDA regulations and NIAID guidelines.

5) distributing final versions of SAE and safety reports to industrial sponsors (if any) and to study investigators and track submission to the investigators' IRBs.

6) developing, implementing and maintaining quality control/assurance procedures and ongoing training of clinical site staff to ensure consistency, completeness and accuracy of SAE reporting.

7) generating line listings of all adverse events occurring in each specific CASG study conducted under IND for annual and final reports to the FDA and as requested by the Project Officer.

SEE NOTE TO OFFEROR P

8) distributing the investigator's brochure to clinical sites when NIAID holds the IND for an investigational drug.

9) attending and participating in DMID regulatory workshops to discuss clinical trial coordination and regulatory issues related in clinical trials.

10) tracking the distribution of study drugs to participating sites and, ultimately, the disposition of study drug by those clinical sites as instructed by the PO. The Contractor shall develop a plan for tracking the distribution and ultimate disposition of study drugs, in collaboration with the Project Officer, for all trials where this function is needed.

3. Develop and submit to the NIAID PO, a clinical trial monitoring plan for each study and CASG site, for approval and subsequent implementation.

a. Monitor clinical trial sites participating in CASG studies to ensure completeness and accuracy of study data and adherence with good clinical practice standards, protocol specifications, regulatory requirements and other relevant Federal policies where NIAID holds the IND, unless otherwise instructed. The contractor shall be responsible for developing a monitoring plan for each study and for assuring that the monitors have sufficient clinical background and be trained to effectively perform the required tasks. The Contractor shall provide the monitors with protocol-specific orientation and assignments by the clinical trial specialists, data managers, the protocol chairs and/or other protocol team members, as appropriate, and NIAID

b. provide a thorough review to site personnel of Federal regulations governing informed consent, Institutional Review Boards, responsibilities of sponsors and investigators, and protection of human

subjects from research risks. A explanation of NIAID policies and procedures as provided by the PO, good clinical practices, as appropriate, will also be provided.

c. conduct interim site monitoring visits to participating CASG sites to evaluate selected data elements (as outlined in the clinical trial monitoring plan for each study). In conducting annual (or more often as necessary) or interim site monitoring visits, the Contractor shall:

1) assess the operation and management of the CASG study sites, as appropriate for the study. The assessment may include, but is not limited to:

a) site management
b) communication among clinical technical and administrative staff
c) maintenance of regulatory files
d) adequacy of site facilities, pharmacy, and study equipment including security measures in place to ensure patient confidentiality and standardization of methodologies.

2) Assess site compliance with the requirements for the CASG protocols being conducted, including but not limited to:

a) compliance with the Manual of Procedures (MOP)
b) adherence to inclusion and exclusion criteria
c) reporting of SAE's
d) accuracy, timeliness and completeness of data collection and entry
e) Documentation of study endpoints
f) Clinical records maintenance
g) Study product accountability
h) Appropriate collection, storage and transport of patient samples
i) Accuracy of the data by source document verification

d. Provide continued monitoring of clinical sites that have significant protocol conduct or data collection deficiencies discovered until those deficiencies are corrected as determined by the PO.

e. Submit reports on clinical site performance after each monitoring visit. Summaries of the findings for each site shall be provided to the PO and the appropriate clinical site coordinator within two weeks of the site visit. In addition, if major concerns regarding site performance are noted, the monitor shall notify the PO by telephone as soon as possible. The reports shall identify any site-specific operational issues or problems. In consultation with the principal investigator and NIAID, the Contractor shall formulate actions to be taken to address problems and track the problems until they are resolved.

f. Receive and participate in review of site monitoring reports prepared for studies where the industrial sponsor is conducting site monitoring.

SEE NOTE TO OFFEROR Q (meetings)

SEE NOTES TO OFFERES R, S (samples of work products)

ATTACHMENT I

National Institutes of Health (NIH)
National Institute of Allergy and Infectious Diseases (NIAID)
Division of Microbiology and Infectious Diseases (DMID)

DATA AND SAFETY MONITORING BOARD (DSMB) GUIDELINES

I. Roles and Responsibilities

The Data and Safety Monitoring Board (DSMB) is an independent group of experts that advises DMID and the study investigators. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations to DMID concerning the continuation, modification, or termination of the trial. The DSMB considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study.

The DSMB is responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review, stopping guidelines, unmasking (unblinding) and voting procedures prior to initiating any data review. The DSMB is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

The DSMB should review each protocol for any major concern prior to implementation. During the trial, the DSMB should review cumulative study data to evaluate safety, study conduct, and scientific validity and integrity of the trial. As part of this responsibility, DSMB members must be satisfied that the timeliness, completeness, and accuracy of the data submitted to them for review are sufficient for evaluation of the safety and welfare of study participants. The DSMB should also assess the performance of overall study operations and any other relevant issues, as necessary.

Items reviewed by the DSMB include:

- Interim/cumulative data for evidence of study-related adverse events;
- Interim/cumulative data for evidence of efficacy according to pre-established statistical guidelines, if appropriate;
- Data quality, completeness, and timeliness;
- Performance of individual centers;
- Adequacy of compliance with goals for recruitment and retention, including those related to the participation of women and minorities;
- Adherence to the protocol;
- Factors that might affect the study outcome or compromise the confidentiality of the trial data (such as protocol violations, unmasking, etc.); and,
- Factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics of the study.

The DSMB should conclude each review with their recommendations to DMID as to whether the study should continue without change, be modified, or terminated. Recommendations regarding modification of the design and conduct of the study could include:

- Modifications of the study protocol based upon the review of the safety data;
- Suspension or early termination of the study or of one or more study arms because of serious concerns about subjects' safety, inadequate performance or rate of enrollment;

- Suspension or early termination of the study or of one or more study arms because study objectives have been obtained according to pre-established statistical guidelines;
- Optional approaches for DMID and investigators to consider when the DSMB determines that the incidence of primary study outcomes is substantially less than expected such as recommendations to increase the number of trial centers or extend the recruitment period; and,
- Corrective actions regarding a study center whose performance appears unsatisfactory or suspicious.

Confidentiality must always be maintained during all phases of DSMB review and deliberations. Usually, only voting members of the DSMB should have access to interim analyses of outcome data by treatment group. Exceptions may be made when the DSMB deems it appropriate. DSMB members must maintain strict confidentiality concerning all privileged trial results ever provided to them. The DSMB should review data only by masked study group (such as X vs. Y rather than experimental vs. control) unless or until the DSMB determines that the identities of the groups are necessary for their decision-making. Whenever masked data are presented to the DSMB, the key to the group coding must be available for immediate unmasking.

II. Membership

The membership of the DSMB should reflect the disciplines and medical specialties necessary to interpret the data from the clinical trial and to fully evaluate participant safety. The number of DSMB members depends on the phase of the trial, range of medical issues, complexity in design and analysis, and potential level of risk but generally consists of three to seven members including, at a minimum:

- Expert(s) in the clinical aspects of the disease/patient population being studied;
- One or more biostatisticians; and,
- Investigators with expertise in current clinical trials conduct and methodology.

Ad hoc specialists may be invited to participate as non-voting members at any time if additional expertise is desired. Some trials, depending on the population and nature of the intervention, may well be served by inclusion of a bioethicist on the DSMB, Steering Committee, or Advisory Panel.

DMID staff without direct involvement in study implementation and who meet other membership criteria may participate as ex officio, non-voting members. DMID staff serving in these positions must have a current confidential financial disclosure report on file with the Deputy Ethics Counselor, NIAID. Representatives of the manufacturer (industrial collaborator) of the test substance(s) or any other individual with vested interests in the outcome of the study are not eligible to serve on the DSMB although they may attend open sessions of the DSMB meetings.

Conflict of Interest

No member of the DSMB should have direct involvement in the conduct of the study. Furthermore, no member should have certain financial, proprietary, professional, or other interests that may affect impartial, independent decision-making by the DSMB. Letters of invitation to prospective DSMB and *ad hoc* members should include the following: "Acceptance of this invitation to serve on the xxx DSMB confirms that I do not have any financial or other interest with any of the collaborating or competing pharmaceutical firms or other organizations involved in the study that constitute a potential conflict of interest." In addition, all DSMB and *ad hoc* members will sign a Conflict of Interest certification to that effect at the time they are asked to participate (see Appendix I). At the beginning of every DSMB meeting, DMID program staff or the DSMB Chair will reconfirm that no conflict of interest exists for DSMB members. Interests that may create a potential conflict of interest should be disclosed to the DSMB prior to any discussion. The DSMB will determine how to handle such potential conflict. The

DSMB can require that a member with a potential conflict not vote or take other means deemed appropriate. NIAID may dismiss a member of the DSMB in the event of unmanageable potential conflict.

Selection and Invitation to Participate

The PO holds primary responsibility for the formation of the DSMB unless the Clinical Terms of Award for a grant specifically identify this as the responsibility of the grantee. The PO (or grantee as specified) is responsible for developing the roster of potential DSMB members. Recommendations for proposed members are solicited from many sources. Study investigators and the industrial collaborators should have the opportunity to review the list of proposed members before the candidate's interest and availability are confirmed by the PO (or grantee as specified). The proposed roster of members must be submitted to the Chief, Office of Clinical Research Affairs (OCRA), DMID or designate for review and approval before invitations are issued.

The PO (or grantee as specified) is responsible for identifying the DSMB Chair. He/she may select the Chair or ask DSMB voting members to select the Chair.

Terms of membership are also determined by the PO (or grantee as specified). Participation is generally for the duration of the study. Participation for standing DSMBs convened to monitor multiple protocols or lengthy studies may be for fixed terms. As continuity of review is essential, the duration of fixed terms should be staggered so that no more than one third of the membership changes at any one time.

III. Meetings

The frequency of DSMB meetings depends on several factors including the rate of enrollment, safety issues or unanticipated side effects, availability of data, and, where relevant, scheduled interim analyses. Unless the Clinical Terms of Award for the grant specifically identify this as the responsibility of the grantee, the PO or designee is responsible for convening meetings, selecting a venue, and coordinating the distribution of meeting materials to DSMB members and other meeting participants. The agenda for each meeting is generally developed jointly by the PO, the Principal Investigator (regardless of whether a contract, cooperative agreement, or grant), the study statistician, and DSMB Chair.

The initial DSMB meeting should occur preferably before the start of the trial or as soon thereafter as possible. At this meeting the DSMB should discuss the protocol, set triggers for data review or analyses, define a quorum, and establish guidelines for monitoring the study. Guidelines should also address stopping the study for safety concerns and, where relevant, for efficacy based on plans specified in the protocol. At this meeting, the DSMB should also develop procedures for conducting business (e.g., voting rules, attendance, etc.). DMID staff may discuss DMID's perspective on the study at this initial meeting.

Once a study is implemented, the DSMB should convene as often as necessary, but at least once annually, to examine the accumulated safety and enrollment data, review study progress, and discuss other factors (internal or external to the study) that might impact continuation of the study as designed. A DSMB meeting may be requested by DSMB members, the PO, industrial collaborator, IRB, or study Principal Investigator at any time to discuss safety concerns. Decisions to hold *ad hoc* meetings will be made by the PO and DSMB Chair. Face-to-face meetings are preferable but conference calls or videoconferences are acceptable alternatives with the agreement of the DSMB members and PO. In the event a DSMB member cannot attend a meeting, he/she may receive a copy of the closed session DSMB report (see below) and either participate by conference call or provide written comments to the DSMB Chair for consideration at the meeting.

A. DSMB meeting format

The recommended meeting format consists of three sessions: Open Session, Closed Session, and Closed Executive Session.

1. Open Session
   Issues relating to the general conduct and progress of the study are discussed including adverse events and toxicity issues, accrual, demographic characteristics of enrollees, disease status of enrollees (if relevant), comparability of groups with respect to baseline factors, protocol compliance, site performance, quality control, and timeliness and completeness of follow-up. Any data provided must be presented without grouping by treatment assignment or otherwise by preserving the masking of all subjects. Outcome results must not be discussed during this session.

   DSMB members, voting and *ex officio* members, NIAID staff members and *ad hoc* experts attend this session. The lead investigator and the study biostatistician should be in attendance in order to present results and respond to questions. This session is open to study investigators, coordinating center staff, representatives for industrial collaborators, representatives from the Food and Drug Administration (FDA), and DMID program and regulatory staff.

2. Closed Session
   Grouped safety data and, if appropriate, efficacy data are presented by the study statistician(s) at this session. Grouped data should be presented by coded treatment arm. This session is normally attended only by voting members, study statisticians, and invited *ex officio* members. The DSMB may invite the participation of other individuals for all or part of the session.

3. Closed Executive Session
   This final session involves only DSMB voting members to ensure complete objectivity as they discuss outcome results, make decisions, and formulate recommendations regarding the study. If treatment codes have been made accessible to the DSMB, then the DSMB may unmask the data based on procedures identified in advance.

B. Voting

A quorum, as defined by the DSMB in the initial meeting, must be present either in person or by conference call. After a thorough discussion of DSMB members' opinions and rationale and an attempt to reach clarity regarding individual recommendations, the final recommendations of each DSMB member should be solicited in Closed Executive Session (e*x officio* members shall not vote and shall not be present at this voting session). The final recommendations are recorded and either identified as majority or minority positions or are accompanied by actual vote tallies for each divergent recommendation, i.e., as number of votes for or against a particular action, such as continuing or terminating a study, etc.

IV. Study Reports for DSMB Meetings

It is the responsibility of the PI to ensure that the DSMB is apprised of all new safety information relevant to the study product and the study. This includes providing the DSMB with a copy of the Clinical Investigator's Brochure (CIB) in advance as well as promptly providing all CIB revisions and all safety

reports issued by the sponsor. Summary safety and enrollment data should be forwarded periodically to the DSMB. The DSMB should receive all protocol revisions and may receive other documents relating to the study.

Reports are prepared by the study statistician(s). The study statistician should provide suggested formats or templates for data presentation for the initial meeting of the DSMB. The DSMB and DMID must review and approve the data elements to be presented. At subsequent meetings, additions or modifications to these reports may be directed by the DSMB on a one-time or continuing basis. Written reports should be sent to DSMB members prior to the meeting and should allow sufficient time for review.

Reports for meetings of the DSMB consist of two separate parts: Open Session Report and Closed Session Report. Open Session reports are distributed to DSMB members, selected DMID staff, and other appropriate persons as directed by the DSMB at least one week prior to a scheduled meeting. Closed Session reports are distributed on the same schedule but only to DSMB members and others as designated by the DSMB Chair. The data presented in the reports must reflect both the need for the fullest possible information on trial results and the need to assure reliability and accuracy of the information included.

A. Part 1 (Open Session Report)
   This report provides information on study conduct, as outlined in Section III.A.1 above, such as accrual, appropriate demographic representation, baseline characteristics, protocol compliance, site performance, quality control, and currency of follow-up. General (ungrouped) adverse events and toxicity issues are also included in the open report.

B. Part 2 (Closed Session Report)
   This report may contain data on study outcomes, including safety data and, depending on the study, efficacy data coded by group. It may also contain data from the Open Session report but presented separately for each study arm. Interim analyses of efficacy data are presented only when planned in advance and appropriate statistical criteria for assessing evidence of efficacy have been clearly addressed. Supplemental information may need to be furnished immediately after the meeting if the DSMB decides that such follow-up is needed in order to conclude their deliberations.

   The Closed Session Report is **confidential** and marked accordingly. Copies of reports distributed prior to and during a meeting are collected by the study statistician(s) at the end of the Closed Session. Procedures for securing closed reports distributed to telephone and videoconference participants should be specified in advance of the meeting.

V. Other Reports of Study Progress

Masked safety and enrollment data may be forwarded periodically to all DSMB members or to the member who serves as the Independent Safety Monitor. The DSMB receives all protocol revisions and may receive other documents relating to the study, such as annual reports, manuscripts, and newsletters. Appropriate follow-up procedures, such as for directing concerns or requests for further information to the PO or designated DMID staff, should be identified in advance.

VI. Reports from the DSMB

A. Verbal Report
   At the conclusion of a DSMB meeting, the DSMB should discuss its findings and recommendations with DMID representatives and the study investigators. If DMID is not represented at the meeting, the DSMB Chair should contact DMID immediately after the meeting

to debrief the PO, the Chief, Office of Clinical Research Affairs (OCRA), and Chief, Office of Regulatory Affairs (ORA).

B. Summary Report

The DSMB will issue a written summary report that identifies topics discussed by the DSMB and describes their individual findings, overall safety assessment and recommendations. The rationale for recommendations will be included when appropriate. This report will generally not include confidential information. The DSMB Chair or designee is responsible for drafting, circulating and obtaining approval from other DSMB members within two (2) weeks of the meeting.

The final summary report will be forwarded through the DMID PO to a designated study team representative (usually the Principal Investigator) and to other appropriate DMID staff. The study team representative is responsible for disseminating the DSMB summary report to site investigators who must, in turn, submit the report to their local IRBs. If under an IND, the sponsor will forward the summary report including routine and nominal findings to the Food and Drug Administration (FDA) and to any other industrial collaborators.

C. Closed Session Report (optional)

The DSMB may also prepare confidential minutes that include details of closed session discussions. Meeting minutes are to be held in strict confidence, accessible only to voting members of the DSMB until such time when the study is closed or the DSMB recommends early termination or in the event the minutes are requested by the FDA or NIAID for participant safety reasons or for regulatory purposes.

D. Immediate Action Report

The DSMB Chair will notify the PO of any findings of a serious and immediate nature or recommendations to discontinue all or part of the trial. The PO will immediately inform appropriate DMID staff, including: the Chief, OCRA, the Chief, ORA, and the Deputy Director of DMID or designate. In addition to verbal communications, recommendations to discontinue or substantially modify the design or conduct of a study must be conveyed to DMID in writing by e-mail, fax, or courier on the day of the DSMB meeting. This written, confidential report may contain unmasked supporting data and include the DSMB member's rationale for their recommendations. The report should be submitted to OCRA and ORA for submission to the FDA, if under an IND.

See Appendix IV for the DMID sign-off sheet for the above reports.

VII. Relationship Between DSMBs and IRBs

NIH policy has explicitly identified required communications that must occur between DSMBs and Institutional Review Boards (IRBs) ("Guidance on reporting adverse events to IRBs for NIH-supported multicenter clinical trials" dated June 11, 1999 (http://grants.nih.gov/grants/guide/notice-files/not99-107.html)). The DSMB should provide feedback at regular and defined intervals to the IRBs. After each meeting of the DSMB, the DSMB's Executive Secretary or Chair should send a brief summary report to each investigator. The report should document that a review of data and outcomes across all centers took place on a given date. It should summarize the DSMB members' review of the cumulative toxicities reported from all participating sites without specific disclosure by treatment arm. It should also inform study investigators of the DSMB members' conclusions with respect to progress or need for modification of the protocol. The investigator is required to transmit the report to his/her local IRB.

VIII. Executive Secretary

An Executive Secretary (ES) may be designated to coordinate the effective functioning of the DSMB. The DSMB Chair may designate an ES for DSMBs established by grantees. The PO may serve as the ES for DSMBs. The ES may not vote or be present during Closed or Closed Executive Sessions and should not have access to the closed session reports and materials.

Responsibilities include:

- Coordinating communications between DSMB members and other meeting participants such as *ex officio* and *ad hoc* members;
- Overseeing meeting logistics including: selecting meeting dates and locations, providing reimbursement for per diem and DSMB honorarium, and assisting with other travel arrangements;
- Assisting the DSMB Chair with preparation and dissemination of meeting summary reports and other appropriate non-confidential documents;
- Obtaining conflict of interest statements; and,
- Preparing thank you letters/letters of appreciation to recognize and acknowledge DSMB members' contributions.

IX. Reimbursement

1. Per diem
   DSMB members should be intellectually and financially independent of trial investigators. If the reimbursement of DSMB members for their participation is not directly from the NIAID, then reimbursement must be provided by funds restricted for this purpose. DSMB members will receive per diem and travel expenses in accordance with Standard Government Travel Regulations. Members who are officers or employees of the United States shall not receive compensation for service on the DSMB.

2. Honorarium
   If deemed appropriate by the PO and funds are available, an honorarium of up to $200 per day may be offered to members who are not full-time Federal employees. Members who are employees of the United States Government shall not receive an honorarium for service on the DSMB.

APPENDIX I

NATIONAL INSTITUTES OF HEALTH
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES

CONFLICT OF INTEREST CERTIFICATION
FOR MEMBERS OF DATA AND SAFETY MONITORING BOARDS (DSMB)

Confidential

DSMB for the ABC Trial on XYZ

- I have not been within the past 12 months a part-time, full-time, paid, or unpaid employee of or am not presently negotiating for employment with any organizations that are: (a) involved in the studies under review; (b) whose products or services will be used or tested in the studies under review, or (c) whose products or services would be directly and predictably affected by any outcome of these studies;

- I am not an officer, member, owner, trustee, director, expert advisor, or consultant, i.e., speaker, researcher, contractor, grantee or collaborator, of such organizations;

- I do not have any financial interests or assets that exceed $10,000 in any organizations meeting the above criteria, nor do my spouse or dependent children or domestic partner;

- I do not have any intellectual, proprietary interest in any of the products being reviewed or in products in direct competition with such products; and,

- I have not been involved in any litigation regarding these organizations (e.g., plaintiff, defendant, expert witness).

PLEASE COMPLETE BELOW.

☐ No relevant interests or activities.

☐ I will disclose exception(s) to the DSMB prior to any discussion so that they can be reflected in the minutes along with the DSMB's determination as to how to handle such exception(s).

I will notify the DSMB's Executive Secretary promptly if a change occurs in any interests or activities during the tenure of my responsibilities.

I am aware of my responsibilities for maintaining the confidentiality of any non-public information that I receive or become aware of through this activity, and for avoiding using such information for my personal benefit, the benefit of my associates, or the benefit of organizations with which I am connected or with which I have a financial involvement.

Member's name (please print)	Signature	Date

ATTACHMENT II

National Institutes of Health (NIH)
National Institute of Allergy and Infectious Diseases (NIAID)
Division of Microbiology and Infectious Diseases (DMID)

SAFETY MONITORING COMMITTEE (SMC) GUIDELINES

I. Roles and Responsibilities

The Safety Monitoring Committee (SMC) is an independent group of experts that advises DMID and the study investigators for Phase I and some Phase II trials. **The primary responsibility of the SMC is to monitor participant safety.** The SMC considers study-specific data as well as relevant background information about the disease, test agent, and target population under study.

Prior to the first data review and preferably prior to study initiation, the SMC should define its deliberative processes. These may include event triggers that would call for an unscheduled review, guidelines for stopping or unmasking (unblinding), and voting procedures. The SMC is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

The SMC should review the protocol, including the safety monitoring plan, and identify any major concerns prior to implementation. During the trial the SMC should review:

- Real-time and cumulative safety data for evidence of study-related adverse events;
- Adherence to the protocol;
- Factors that might affect the study outcome or compromise the trial data (such as protocol violations, losses to follow-up, etc.); and,
- Data relevant to proceeding to the next state of the study, if applicable.

Other relevant issues, such as pharmacokinetics and/or immunogenicity data, data quality, site performance, recruitment and retention, and factors external to the study may also need to be considered.

The SMC should conclude each review with each member's recommendation to DMID as to whether the study should continue, be modified, or be terminated. Recommendations regarding modification of the design and conduct of the study may include corrective actions when performance is unsatisfactory, or recommendations to advance to the next dose in a dose escalation study, for example, or to the next stage in product testing.

Confidentiality must always be maintained during all phases of SMC review and deliberations. For masked studies, only members of the SMC and study biostatisticians should have access to the emerging study data broken down by treatment group (even if the group identities are masked). Exceptions may be made when the SMC deems it appropriate. Whenever masked data are presented to the SMC, the key to the group coding must be available for immediate unmasking.

II. Membership

The membership of the SMC should reflect the disciplines and medical specialties necessary to interpret the data from the clinical trial and to fully evaluate participant safety. The SMC generally consists of at least three voting members. Membership should include an Independent Safety Monitor (ISM) from one or more participating sites, expertise in the clinical aspects of the disease/patient population being studied, and expertise in current clinical trials conduct and methodology.

Consideration should be given to including a biostatistician if statistical tests of the data will be evaluated. A biostatistician, as well as other specialists, may be invited to participate as non-voting members on an a*d hoc* basis at any time if additional expertise is desired. SMC and ad hoc members may be from the principal investigator's institution or from other participating sites but should not be directly involved with the trial or under the

supervision of the trial investigator. Furthermore, the SMC members should generally be in a different organizational group than the Principal Investigator (PI).

DMID and other NIH staff who are not involved in the study may also participate as voting members. However, members of the sponsoring DMID Branch are discouraged from having voting privileges. Project Officers or other NIH staff involved in the study may participate as ex officio, non-voting members. Representatives of the manufacturer (industrial collaborator) of the test substance(s) or any other individual with vested interests in the outcome of the study are not eligible to serve on the SMC as ex officio or voting members.

Conflict of Interest

No member of the SMC should have direct involvement in the conduct of the study. Furthermore, no member should have certain financial, proprietary, professional, or other interests that may affect impartial, independent decision-making by the SMC. Letters of invitation to prospective SMC and *ad hoc* members should include the following: "Acceptance of this invitation to serve on the xxx SMC confirms that I do not have any financial or other interest with any of the collaborating or competing pharmaceutical firms or other organizations involved in the study that constitute a potential conflict of interest." In addition, all SMC and *ad hoc* members will sign a Conflict of Interest certification to that effect at the time they are asked to participate (see Appendix II). At the beginning of every SMC meeting, DMID program staff or the SMC Chair will reconfirm that no conflict of interest exists for SMC members. Interests that may create a potential conflict of interest should be disclosed to the SMC prior to any discussion. The SMC will determine how to handle such potential conflict. The SMC can require that a member with a potential conflict not vote or take other means deemed appropriate. NIAID may dismiss a member of the SMC in the event of unmanageable potential conflict.

Selection and Invitation to Participate

The NIAID Program or Project Officer (PO) holds primary responsibility for the formation of the SMC, unless the Clinical Terms of Award for a grant specifically identifies this as the responsibility of the grantee. The PO (or grantee as specified) is responsible for developing the roster of potential SMC members. Recommendations for proposed members may be solicited from many sources. The proposed roster of members must be submitted to the Chief, Office of Clinical Research Affairs (OCRA) or designee for review and approval before invitations are issued.

The PO (or grantee as specified) is responsible for identifying the SMC Chair. He/she may either select the Chair directly or ask SMC voting members to select the Chair.

III. Meetings

The structure and operating procedures for a SMC are usually less formal than that of a DSMB. The initial SMC meeting should occur before the start of the trial or as soon thereafter as possible. DMID staff may discuss DMID's perspective on and expectations for the study at this initial meeting. At this meeting the SMC should discuss the protocol, set triggers for data review, define a quorum, and establish guidelines for monitoring the study. The SMC should decide which member(s) should receive reports of serious adverse events in real time and determine if on-site review of clinical records might be needed. Guidelines for stopping the study for safety concerns should be established. At this meeting, the SMC should also develop procedures for conducting business (e.g., data required for review, voting rules, attendance, etc.). Teleconference calls may often be an appropriate means for conducting meetings.

Based on initial discussions, the SMC should decide whether to meet on a regular basis or only with the occurrence of adverse events. In many cases, it may be appropriate for meetings to be convened on an *ad hoc* basis based on the occurrence of adverse events. Scheduling of meetings should be based on the magnitude of the perceived risks, decision points in the protocol (e.g., the decision to move to a higher dose), rate of enrollment, or problems that occur during the progress of the study. The SMC may be asked for advice at the conclusion of the study about whether to proceed with the next phase of development of the study product.

The PO or designee is responsible for convening meetings or conference calls as needed unless the Clinical Terms of Award for a grant specifically identifies this as the responsibility of the grantee. However, meetings may be requested for cause by any member of the SMC, the investigator, IRB, the manufacturer, or DMID. The investigator will be responsible for ensuring the distribution of materials for review to SMC members and other meeting participants.

A. SMC meeting format

The recommended meeting format may consist of the following sessions: Open Session, Closed Session (optional), and Closed Executive Session.

1. Open Session
   Occurrences of adverse events and toxicity issues are reviewed. Issues relating to the general conduct and progress of the study may also be considered. Outcome results must not be discussed during this session and, if the study is masked, no study group-specific data should be reviewed or discussed.

   SMC members, voting and *ex officio* members, NIAID staff members, and *adhoc* experts attend and participate in this session. The lead investigator and study statistician, if applicable, should attend and participate to present results and respond to questions. This session is open to study investigators, coordinating center staff, representatives for industrial collaborators, representatives from the Food and Drug Administration (FDA), and NIH program and regulatory staff.

2. Closed Session (optional; generally only required if the study is masked)
   Study group-specific data, masked if so specified, are presented at this session. This session is normally attended only by voting members, study statistician, and *ex officio* members.

3. Closed Executive Session
   This final session involves only voting members to ensure complete independence for making decisions and formulating independent recommendations. The SMC may unmask the data based on procedures identified in advance.

B. Voting

A quorum, as defined by the SMC in the initial meeting, must be present either in person or by conference call. After a thorough discussion of SMC members' opinions and rationale and a joint attempt to reach clarity regarding individual recommendations, the final recommendations of each SMC member should be solicited in Closed Executive Session (e*x officio* members shall not vote and shall not be present at this voting session). The final recommendations are recorded and either identified as majority or minority positions or are accompanied by actual vote tallies for each divergent recommendation, i.e., as number of votes for or against a particular action, e.g., continue study, terminate study, etc.

IV. Study Reports for SMC Review

It is the responsibility of the PI to ensure that the SMC is apprised of all new safety information relevant to the study product and the study. This includes providing the SMC with a copy of the Clinical Investigator's Brochure (CIB) in advance as well as promptly providing all IB revisions and all safety reports issued by the sponsor. Summary safety and enrollment data should be forwarded periodically to the SMC. The SMC should receive all protocol revisions and may receive other documents relating to the study.

Reports are prepared by the study statistician or else the investigator. The general content for reports to the SMC is as determined by the SMC at the initial meeting. The SMC and DMID must also review and approve the actual

data elements to be presented. At each meeting, additions or modifications to these reports may be directed by the SMC on a one-time or continuing basis. Distribution of written reports should allow sufficient time for review.

Reports for meetings of the SMC will consist of the Open Session Report and, if required, a Closed Session Report. Open Session reports are distributed to SMC members, selected DMID staff, and other appropriate persons as directed by the SMC. Closed Session reports are distributed only to SMC members and others as designated by the SMC. The Closed Session Report may contain study group-specific data and should be marked **confidential** and handled accordingly.

V. Other Reports of Study Progress

Safety and enrollment data should be forwarded periodically to all SMC members. The SMC should also receive all protocol revisions and may receive other documents relating to the study, such as annual reports, manuscripts, and newsletters.

VI. Reports from the SMC

C. Verbal Report
At the conclusion of a SMC meeting, the SMC should discuss its findings and recommendations with DMID representatives and the study investigators. If DMID is not represented at the meeting, the SMC Chair should contact DMID immediately after the meeting to debrief the PO.

B. Summary Report
The SMC will periodically issue a written summary report that identifies topics discussed by the SMC and describes their individual findings, overall safety assessment, and recommendations. This would generally occur after each meeting but SMCs that meet on a more frequent basis may summarize more than one meeting in each report. The rationale for recommendations will be included when appropriate. This report will not include confidential information. The SMC Chair or designee is responsible for preparing and distributing the report.

Unless otherwise specified, the summary report will be forwarded through the DMID PO to a designated study team representative (usually the Principal Investigator) and to other appropriate DMID staff. The study team representative is responsible for disseminating the SMC summary report to site investigators and, IND sponsors and industrial collaborators, if any. Site investigators must, in turn, submit the reports to their respective IRBs in accordance with local IRB policy and other industrial collaborators. If under an IND, the sponsor (IND holder) will forward the summary report to the FDA.

C. Closed Session Minutes (optional)
The SMC may also prepare confidential minutes that include details of closed session discussions. Meeting minutes are to be held in strict confidence, accessible only to voting members of the SMC until a) such time when the study is closed, b) if the SMC recommends early termination, or c) if the minutes are requested by the FDA or NIAID for patient safety or regulatory purposes.

D. Immediate Action Report
The SMC Chair will notify the PO of any findings of a serious and immediate nature, such as if the SMC recommends that all or part of the trial be discontinued. The PO will immediately inform appropriate DMID staff, including: the Chief, Office of Clinical Research Affairs (OCRA), the Chief, Office of Regulatory Affairs (ORA), and the Deputy Director of DMID or designee. In addition to verbal communications, recommendations to discontinue or substantially modify the design or conduct of a study must be conveyed to DMID in writing on the day of the SMC meeting. This written, confidential briefing may contain unmasked supporting data and should include the SMC members' rationale for its recommendations. The written briefing should be submitted to OCRA and ORA for submission to the FDA, if under an IND.

See Appendix IV for the DMID sign-off sheet for the above reports.

NOTE: DO NOT USE FOR DSMB

NATIONAL INSTITUTES OF HEALTH
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES

CONFLICT OF INTEREST CERTIFICATION FOR MEMBERS OF SAFETY MONITORIG COMMITTEES (SMC)

Confidential

SMC for the ABC Trial on XYZ

- I have not been within the past 12 months a part-time, full-time, paid, or unpaid employee of or am not presently negotiating for employment with any organizations that are: (a) involved in the studies under review; (b) whose products or services will be used or tested in the studies under review, or (c) whose products or services would be directly and predictably affected by any outcome of these studies;

- I am not an officer, member, owner, trustee, director, expert advisor, or consultant, i.e., speaker, researcher, contractor, grantee or collaborator, of such organizations;

- I do not have any financial interests or assets that exceed $10,000 in any organizations meeting the above criteria, nor do my spouse or dependent children or domestic partner;

- I do not have any intellectual, proprietary interest in any of the products being reviewed or in products in direct competition with such products; and,

- I have not been involved in any litigation regarding these organizations (e.g., plaintiff, defendant, expert witness).

PLEASE COMPLETE BELOW.

☐ No relevant interests or activities.

☐ I will disclose exception(s) to the SMC prior to any discussion so that they can be reflected in the minutes along with the SMC's determination as to how to handle such exception(s).

I will notify the DMID Program/Project Officer promptly if a change occurs in any interests or activities during the tenure of my responsibilities.

I am aware of my responsibilities for maintaining the confidentiality of any non-public information that I receive or become aware of through this activity, and for avoiding using such information for my personal benefit, the benefit of my associates, or the benefit of organizations with which I am connected or with which I have a financial involvement.

Member's name (please print)	Signature	Date

ATTACHMENT III

National Institutes of Health (NIH)
National Institute of Allergy and Infectious Diseases (NIAID)
Division of Microbiology and Infectious Diseases (DMID)

INDEPENDENT SAFETY MONITOR (ISM) GUIDELINES

I. Roles and Responsibilities

The Independent Safety Monitor (ISM) is a physician with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. This is accomplished by review of adverse events, immediately after they occur, with follow-up through resolution. The ISM evaluates individual and cumulative participant data when making recommendations regarding the safe continuation of the study.

An ISM could be the sole monitor for the study or may perform this role as a member of a Data and Safety Monitoring Board (DSMB) or Safety Monitoring Committee (SMC). An ISM is appropriate as the sole independent safety monitor for small, early phase studies considered to be low risk, such as some pharmacokinetics or immunogenicity studies, or other studies of short duration. DSMBs and SMCs should consider the need to designate one or more members as ISM(s). In the case of DSMBs, the ISM focus may be directed at serious adverse events (SAEs) rather than all adverse events (AEs).

II. Selection and Invitation to Participate

The ISM should be selected based on relevant study-related expertise. Participation is for the duration of the study. The ISM should be able to readily access participant records in real time. He/she is generally a member of the participating institution's staff . The ISM should not be under the direct supervision of the investigator and should preferably be from a different organizational group.

Conflict of Interest

No ISM should have direct involvement in the conduct of the study. Furthermore, no ISM should have certain financial, proprietary, professional, or other interests that may affect impartial, independent decision-making. Letters of invitation to prospective ISMs should include the following: "Acceptance of this invitation to serve as the xxx ISM confirms that I do not have any financial or other interest with any of the collaborating or competing pharmaceutical firms or other organizations involved in the study that constitute a potential conflict of interest." In addition, all ISMs will sign a Conflict of Interest certification to that effect at the time they are asked to participate (see Appendix III).

If the ISM performs this role as a member of a DSMB or SMC, DMID program staff or the DSMB or SMC Chair (as appropriate) will reconfirm that no conflict of interest exists for the ISM at the beginning of every DSMB or SMC meeting. Interests that may create a potential conflict of interest should be disclosed to the DSMB or SMC prior to any discussion. The DSMB or SMC will determine how to handle such potential conflict. The DSMB or SMC can require that an ISM with a potential conflict not vote or take other means deemed appropriate.

If the ISM is acting as the sole independent monitor, the DMID Program/Project Officer (PO) will reconfirm prior to any review of data or at least annually that no conflict of interest exists. Interests that may create a potential conflict of interest should be disclosed to the DMID PO prior to any review of data. The DMID PO, in consultation with the Chief, Office of Clinical Research Affairs (OCRA), will determine if the relationship is in conflict or gives the appearance of a conflict such that the individual should not serve as the ISM. DMID will

determine how to handle such potential conflict. DMID can require that an ISM with a potential conflict not vote or take other means deemed appropriate. NIAID may dismiss an ISM in the event of unmanageable potential conflict.

III. Study Materials for ISM Review

The primary focus of the ISM is to independently review all adverse events and thoroughly investigate those considered serious and unexpected. As the sole monitor, the ISM accomplishes this by evaluating all adverse events against the known safety profile of the study product. Clinical and laboratory data, clinical records, and other study-related records should be made available for ISM review. If necessary, special reports are prepared by the investigator or study statistician.

It is the responsibility of the PI to ensure that the ISM is apprised of all new safety information relevant to the study product and the study. This includes providing the ISM with a copy of the Clinical Investigator's Brochure (CIB) in advance as well as promptly providing all CIB revisions and all safety reports issued by the sponsor. Summary safety and enrollment data should be forwarded periodically to the ISM. The ISM should receive all protocol revisions and may receive other documents relating to the study.

IV. Reports from the ISM

The following reports are submitted by the ISM when acting as the sole independent monitor; otherwise the ISM operates under the guidelines of the DSMB or SMC).

A. Review Report

According to pre-specified criteria agreed upon by the DMID Program or Project Officer (PO), the ISM should communicate in writing his/her findings, any concerns and recommendations to DMID representatives and the study investigators**.** Unless otherwise specified, the written report will be forwarded through the DMID PO to a designated study team representative (usually the Principal Investigator) and to other appropriate DMID staff including the Chief, Office of Clinical Research Affairs (OCRA) and the Chief, Office of Regulatory Affairs (ORA). The study team representative is responsible for disseminating the ISM summary report to any other site investigators and each investigator must, in turn, submit the report as per local IRB policy. If under an IND, the sponsor will forward the summary report to the FDA and to any other industrial collaborators.

B. Immediate Action Report

The ISM will notify the PO of any findings of a serious and immediate nature including any recommendations to discontinue all or part of the trial, and the PO will immediately inform the Chief, OCRA, the Chief, ORA, and Deputy Director of DMID or designate. In addition to verbal communications, recommendations to discontinue or substantially modify the design or conduct of a study must be conveyed to DMID in writing on the day of the ISM review. This written, confidential report may contain unmasked supporting data and include the ISM's rationale for the recommendations. The report should be submitted to OCRA and ORA for submission to the FDA, if under an IND.

See Appendix IV for the DMID sign-off sheet for the above reports.

NOTE: DO NOT USE FOR DSMB, SMC

NATIONAL INSTITUTES OF HEALTH
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES

CONFLICT OF INTEREST CERTIFICATION
FOR INDEPENDENT SAFETY MONITOR (ISM)

Confidential

ISM for the ABC Trial on XYZ

- I have not been within the past 12 months a part-time, full-time, paid, or unpaid employee of or am not presently negotiating for employment with any organizations that are: (a) involved in the studies under review; (b) whose products or services will be used or tested in the studies under review, or (c) whose products or services would be directly and predictably affected by any outcome of these studies;

- I am not an officer, member, owner, trustee, director, expert advisor, or consultant, i.e., speaker, researcher, contractor, grantee or collaborator, of such organizations;

- I do not have any financial interests or assets that exceed $10,000 in any organizations meeting the above criteria, nor do my spouse or dependent children or domestic partner;

- I do not have any intellectual, proprietary interest in any of the products being reviewed or in products in direct competition with such products; and,

- I have not been involved in any litigation regarding these organizations (e.g., plaintiff, defendant, expert witness).

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☐ No relevant interests or activities.

☐ I will disclose exception(s) to the DSMB or SMC (as appropriate) prior to any discussion so that they can be reflected in the minutes along with the DSMB's determination as to how to handle such exception(s). If acting as the sole monitor, I will disclose exception(s) to the DMID Program/Project Officer prior to review of data so that they can be reflected in the review report along with DMID's determination as to how to handle such exception(s).

I will notify the DMID Program/Project Officer promptly if a change occurs in any interests or activities during the tenure of my responsibilities.

I am aware of my responsibilities for maintaining the confidentiality of any non-public information that I receive or become aware of through this activity, and for avoiding using such information for my personal benefit, the benefit of my associates, or the benefit of organizations with which I am connected or with which I have a financial involvement.

Member's name (please print)	**Signature**	**Date**

National Institutes of Health (NIH)
National Institute of Allergy and Infectious Diseases (NIAID)
Division of Microbiology and Infectious Diseases (DMID)

POLICY AND GUIDELINES FOR DATA AND SAFETY MONITORING

I. Introduction

The Division of Microbiology and Infectious Diseases (DMID) supports, through both the contract and grant mechanism, a large number of clinical studies and trials. All DMID studies are conducted in accordance with DHHS regulations 45 CFR 46, which provide for the protection of study participants. To assure that procedures are in place to protect the safety of participants while assuring the validity and integrity of the study, DMID has adopted policies which mandate that a safety monitoring plan be established for all clinical trials. This requirement pertains to all studies that evaluate investigational test articles, studies in which there is a potential for harm to participants, and other studies in which independent assessments are required to assure objectivity. These policies apply to all DMID-sponsored research, regardless of funding mechanism, and are consistent with the NIH Policy for Data and Safety Monitoring issued on June 10, 1998 (http://grants.nih.gov/grants/guide/notice-files/not98-084.html) and Further Guidance on Data and Safety Monitoring for Phase I and Phase II Trials issued on June 5, 2000 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html). The NIH policy requires that each Institute and Center (IC) have a system for the appropriate oversight and monitoring of the conduct of clinical trials that ensures the safety of participants and the validity and integrity of the data. The policy further elaborates that monitoring should be commensurate with risks and with the size and complexity of the trials. Generally, the NIH requires Data and Safety Monitoring Boards (DSMBs) for Phase III clinical trials. For earlier trials (Phase I and II), a DSMB may be appropriate if the studies have multiple clinical sites, are blinded (masked), or employ particularly high-risk interventions or vulnerable populations. For other Phase I and Phase II trials, alternative formats may be utilized for monitoring.

This document provides further guidance for monitoring of all clinical trials supported by DMID. In addition to the general guidelines, specific guidelines for each of three different formats for independent monitoring that are described in section III below are attached.

II. Purpose

The purpose of data and safety monitoring is to provide an independent and objective review of interim safety and, if appropriate, efficacy data. In addition, data and safety monitoring can provide independent and objective review of the overall conduct of the study in order to protect the safety of volunteers and to ensure the integrity of the data. Monitoring bodies are advisory to DMID and their recommendations, while given careful consideration, are not binding. The primary charge to the advisory members is to monitor safety, study conduct, and study progress as well as accumulated data. They also provide advice to DMID and the study investigators as to the appropriateness of continuing the study as designed. In certain situations, independent monitoring boards may also be asked to provide recommendations concerning, for example, the need for extended follow-up or for initiation of related studies based on their findings.

All clinical research that entails greater than "minimal risk" requires independent monitoring. "Minimal risk" is defined in 45 CFR 46, Section 102 (i) as: a risk where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than doing so as part of a routine physical examination.

III. Formats for Monitoring

Three standard formats are available for independent monitoring of DMID-sponsored studies: 1) Data and Safety Monitoring Board (DSMB), 2) Safety Monitoring Committee (SMC), and 3) Independent Safety Monitor (ISM).

Each is briefly summarized below. Detailed guidelines for the establishment and functioning of each are provided in Attachments I, II, and III, respectively. The DMID Program or Project Officer (PO refers to either) who has lead programmatic responsibility for a study, in consultation with the Chief, Office of Clinical Research Affairs (OCRA), determines which of these types of monitoring is appropriate based on the particular study design, study population, research environment, and degree of risk anticipated.

1. Data and Safety Monitoring Board. A DSMB is an independent group of experts that advises DMID and the study investigators. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations to DMID concerning the continuation, modification, or termination of the trial. DSMBs meet regularly and whenever any special need arises to review study conduct and cumulative study data, and to recommend whether the study should continue without change, be modified, or be terminated. Recommendations to modify, suspend or terminate a trial may be based on any aspects of the trial it considers. A DSMB member's recommendation to terminate a trial based on finding efficacy (i.e., early rejection of the null hypothesis concerning the primary endpoint) requires statistical adjustments for interim evaluations and thus requires a pre-specified plan for interim statistical analysis. Therefore, it is essential that the DSMB for such trials include a member with appropriate statistical expertise. All DMID-sponsored Phase III trials are subject to DSMB review. DSMB oversight should be considered for other clinical trials, such as masked (blinded) Phase I and Phase II trials and for some unmasked Phase II trials.

2. Safety Monitoring Committee (SMC)

   The Safety Monitoring Committee (SMC) is an independent group of experts that advises DMID and the study investigators for many Phase I and smaller Phase II trials. The primary responsibility of the SMC is to monitor participant safety. Roles and responsibilities are similar to those of a DSMB except interim evaluations of efficacy are not performed. Investigators and Pos should consider having at least one member of the SMC serve as an Independent Safety Monitor (see below). The SMC must be able to convene on an ad hoc basis when immediate safety concerns arise. Its members may be from the investigator's institution or other participating sites but should not be directly involved with the trial or under the investigator's supervision. It may be sufficient for a SMC to rely on an ad hoc or study statistician to assist in interpreting the results, thereby obviating the need to have a statistician as a member.

3. Independent Safety Monitor (ISM)

   The Independent Safety Monitor (ISM) is a physician with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. This is accomplished by review of adverse events, immediately after they occur, with follow-up through resolution. The ISM evaluates individual and cumulative participant data when making recommendations regarding safe continuation of the study.

   An ISM could be the sole monitor for the study or may perform this role as a member of a DSMB or SMC. An ISM is appropriate as the sole independent safety monitor for small, early phase studies considered to be low risk, such as some pharmacokinetics or immunogenicity studies, or other studies of short duration. DSMBs, the ISM focus may be directed at serious adverse events rather than all adverse events.

IV. Relationship Between Safety Monitoring Groups and Institutional Review Boards (IRB)

Once a safety monitoring group is established, each of the relevant Institutional Review Boards (IRBs) should be informed of the operating procedures with regard to data and safety monitoring (e.g., who, what, when, and how monitoring will take place). This information will serve to assure the IRB that the safety of the research participants is appropriately monitored. If the IRB is not satisfied with the monitoring procedures, it should request modifications. While it is recognized that it may not be possible to satisfy every IRB completely, IRB comments should be considered seriously.

Implementation procedures are provided in the NIH policy on "Guidance on Reporting Adverse Events to IRBs for NIH-supported Multicenter Clinical Trials" dated June 11, 1999 (http://grants.nih.gov/grants/guide/notice-files/not99-107.html). While this policy applies specifically to DSMBs, applicability should be considered for all monitoring formats.

V. International Clinical Trials

General principles for data and safety monitoring apply to all international studies. Procedures may need to be modified to accommodate the policies, regulations, and cultural preferences of the host country.

2002 CASG ACTIVE STUDIES

ADULT

1. A Randomized Phase III Study to Evaluate the Safety and Efficacy of Ribavirin Inhaled Solution in Preventing Progression of Upper Respiratory Tract Respiratory Syncytial Virus (RSV) Infection to RSV Pneumonia in Blood and Bone Marrow Transplant (BMT) Recipients.

2. A Phase III Double-Blind, Placebo-Controlled Trial of Long-Term Therapy of Herpes Simplex Encephalitis (HSE): An Evaluation of Valacyclovir.

3. A Randomized, Open-Label Phase I/II Study to Evaluate the Safety and Pharmacokinetics of Hepatitis C Immune Globulin (Human), Civacir ^{TM} in Liver Transplant Recipients.

PEDIATRIC

1. Evaluation of High Dose Acyclovir in the Treatment of Neonatal HSV Infection (Phase I/II). (Closed to enrollment. Patient follow-up continuing).

2. A Placebo-Controlled Phase III Evaluation of Suppressive Therapy with Oral Acyclovir Suspension Following Neonatal Herpes Simplex Infections involving the Central Nervous System.

3. A Placebo-Controlled Phase III Evaluation of Suppressive Therapy with Oral Acyclovir Suspension Following Neonatal Herpes Simplex Infections Limited to the Skin, Eye and Mouth.

4. A Double-Blind, Placebo-Controlled, Virologic Efficacy Trial of Pleconaril in the Treatment of Infants with Enteroviral Meningitis. (Closed to enrollment, patient follow-up continuing).

5. A Double-Blind, Placebo-Controlled, Virologic Efficacy Trial of Pleconaril in the Treatment of Infants with Enteroviral Sepsis Syndrome.

6. A Phase II Pharmacokinetic and Pharmacodynamic Evaluation of Oral Valganciclovir in Neonates with Symptomatic Congenital Cytomegalovirus (CMV) Infection Involving the Central Nervous System.

7. A Follow-up Assessment of Subjects Who Received Ganciclovir (Dihydroxypropoxymethyl Guanine (DHPG) During the Phase I/II Study to Evaluate the Safety and Efficacy of Ganciclovir Treatment for Congenital Cytomegalovirus (CMV) Infections.

Notes To Offerors

Clinical Trials for Antiviral Therapies
DMID-03-08

GENERAL NOTES TO OFFERORS:

A. In order to adequately fulfill the requirements of this Statement of Work, the Offeror will need expertise in the areas of antiviral therapy (including drug and immunotherapies), clinical trials, human viral infections (particularly, herpesvirus infections), biostatistics, virology and immunology. Evidence of this expertise shall be included in the proposal. If the Offeror does not have all expertise in house, the plan should identify which components will be subcontracted and identify the expertise of the subcontractor.

B. A well trained, committed and balanced team of coordinating center staff and group of collaborators with demonstrated experience and success in conduct of single center and multi-center trials should be identified. The Principal Investigator (PI) shall have an M.D. and/or Ph.D. degree and shall be experienced in clinical trials involving appropriate patient populations consistent with the type of study outlined in the RFP. The team of professional personnel, (PI, physicians, nurses, biostatisticians, laboratory director, etc.) shall have composite expertise in viral diseases, multicenter clinical trials, good clinical practice, conduct of clinical studies of rare viral diseases in special populations, including but not limited to pediatric populations, data management, biostatistics, laboratory assay development and characterization, and clinical protocol development and management. The technical personnel should be trained and experienced in performing assays and laboratory procedures. The support staff should possess the requisite experience to perform their clerical, administrative, and regulatory duties. A detailed organizational chart should be provided for the Central Unit that shows the administrative structure, supervisory and oversight roles, and the interactions among groups. A maximum 2 page Biosketch or Curricula Vitae of all proposed professional personnel must be included in the proposal.

C. Direct patient care costs will not be reimbursed as allowable costs under this contract. A set amount for reimbursement on a per patient basis to cover expenses incurred by each study is appropriate. Final payment to a subcontractor should not be made until completed case report forms have been received by the Central Unit.

D. Proposals should describe how the Offeror will develop, refine, and implement the clinical trials in the context of recommendations by the expert panel.

E. Proposals should outline reporting policies to ensure that data are reported in a timely manner. This should include the reporting of information to the Central Unit and to the PO in accordance with IND requirements of the Food and Drug Administration, in addition to reporting of scientific results for publication. Procedures for the determination of publication authorship should be addressed for multicenter trials. The facilities and equipment to be used for data management should be described.

F. Offerors should discuss approaches to identification of clinical sites and recruitment of sites for complex studies for rare diseases. The Offerors should describe how sites will be selected and what criteria sites must meet to participate in CASG trials. The Offerors should describe what, if any, role site investigators will have in protocol development. Offerors should discuss approaches to limit the number of low recruiting centers to reduce the administration burden on the Central Unit.

WORK STATEMENT NOTES: (specific plans requested below should be attached to the proposal as appendices and listed in the table of contents of the proposal)

G. For evaluation purposes only, the Offeror should submit a sample research plan that discusses the current status of therapy for herpesvirus diseases as well as the advantages and disadvantages of therapeutic alternatives and strategies. The PI should indicate which studies in the plan are the highest priority. High medical priorities should be included whether or not a candidate experimental therapeutic agent is presently available if it is reasonable to assume one might become available. This discussion should include the potential utility of new chemotherapeutic and immunomodulatory agents, combination and sequential therapies and different delivery systems, if appropriate. The research plan should identify important gaps in knowledge of natural history of herpesvirus diseases, particularly in special populations and identify methods to address those gaps, as well as important gaps in safety information of therapeutics for special patient populations that may be addressed in clinical trials. The research plan should discuss the potential for validation of surrogate markers for clinical product development, mechanisms to address development of resistance to antiviral therapies (both detection and medical management).

H. A list of ongoing studies that will likely continue for some period of time under the new contract is attached. It is estimated that one to three new studies will be implemented each year of the contract as other studies are closed or completed. At least two of the studies will be therapeutic trials. One will be natural history/pathogenesis type of study.

I. For budget purposes, it is anticipated that up to 100 clinical sites may be needed for any year of the contract to accomplish all the studies in an anticipated research portfolio that encompasses rare viral diseases. Because the diseases to be studied are rare, it is anticipated that a total of 150 subjects will be enrolled in all studies each year; however up to 1000 patients may be required to be screened for meeting enrollment criteria each year. Screening and recruitment for most studies will span 1-4 years.

J. It is likely that all studies will require follow-up of patients for up to one year. Some studies may require 3 year follow-up of patients.

K. The Offeror should provide a research plan that discusses the methods for incorporation of study recommendations by the expert panel and how studies will be prioritized/re-prioritized to accomplish new recommendations.

L. Key personnel must include a senior investigator with established clinical pharmacology expertise as evidenced by a degree such as Pharm.D., Ph.D. or MD with documented experience in the design and analysis of exposure (pharmacokinetics) and exposure/response (pharmacokinetic/pharmcodynamic) clinical studies.

M It is anticipated that Biostatistical staff time required for assistance on other (non-CASG) DMID DSMBs, SMCs will be less than 8 hours per month.

N. The Central Laboratory should have the demonstrated capability to develop and characterize virologic assays for herpesvirus infections. The lab should have the ability to track samples from multicenter studies and maintain a database with the ability to track samples for which the patients have consented for furture use of their specimens. Other types of virologic assays or immunologic assays may be sent to commercial labs for analysis.

O. Key personnel must include an experienced project manager to oversee protocol development, implementation and review.

P. NIAID will assume the responsibility for filing all INDs. All protocol submissions are coordinated through the PO. FDA and NIAID guidelines for the conduct of clinical trials will be implemented. Final determination of the clinical trials to be performed will be made by the PO. It is anticipated that all of the CASG studies, other than natural history/pathogenesis studies, will be conducted under an IND.

Q. For planning purposes, include in the Business Proposal, the operational and travel costs to attend the following meetings: the annual investigators meeting, operational staff meeting with the PO semi-annually, one regulatory meeting. The annual investigators' meeting should include travel costs for all key contract personnel, one investigator from each study site, and up to 6 members of the expert panel if needed. The key operations staff should plan to meet semi-annually with the project officer. Key study personnel should plan to attend one regulatory meeting at DMID's request per year. The PI, and co-PIs should plan to attend the meeting with the expert panel each year. All of these meetings will be held in the Washington DC area. The Business proposal should also include expected costs for clinical site visits by Central Unit personnel, training sessions, and protocol development meetings and study start-up meetings. It is estimated that up to 20 clinical site visits, 5 training sessions two protocol development meetings and two study start-up meetings may be needed annually.

R. For evaluation purposes, the Offeror should provide a sample protocol and select case report forms and a manual of procedures for the conduct of that sample protocol.

S. For evaluation purposes, the Offeror should provide examples of the Central Laboratories capability in developing methods to assess the presence of a viral infection in the clinic, to assess the development of resistance to an antiviral therapy and to assess a surrogate marker for efficacy.

Reporting Requirements
Clinical Trials for Antiviral Therapies
RFP DMID-03-08

The Contractor shall submit to the Contracting Officer (CO) and the Project Officer (PO) technical progress reports covering the work accomplished during each reporting period. The exact submission schedule will be negotiated and established in the contract document. These reports shall be factual and prepared in accordance with the following format:

A. Technical Reports

In addition to those reports required by the other terms of this contract, the Contractor shall prepare and submit the following reports in the manner stated below:

1. Semi-annual Technical Progress Report. The Contractor shall prepare and submit two (2) paper copies and one (1) electronic copy of semi-annual report 30 days following the end of each sixth month period. Initially the electronic copy should contain PDF files on a CD-ROM. As technology changes, the electronic medium for submission may change at the request of the PO. One (1) paper copy and the electronic copy should be sent to the PO and one (1) paper copy to the CO. The report shall include the following specific information.

    a. A cover page that lists the contract number and title, the period of performance being reported, the contractor's names and address, the authors(s), and the date of submission.

    b. Section I. An introduction covering the purpose and scope of the contract effort.

    c. Section II. A description of overall progress plus a separate description for each task or other logical segment of work on which effort was expended during the report period.

    d. Section III. A description of current technical or substantive performance and any problems encountered and/or which may exist along with proposed corrective action. Each clinical study should be reported separately, according to the number assigned by the PO. An explanation of any difference between planned progress and actual progress, why the differences have occurred, and if behind planned progress, what corrective steps are planned. The status of all ongoing trials shall be summarized in terms of study results and publications. A summary assessment of the performances of all sites shall be included and is to address patient accrual and retention on protocols, adherence to protocols and research standards, and timeliness and accuracy of completion of case report forms. The summary shall document how accrual meets the current guidelines for inclusion of minorities and both genders.

    e. An anticipated work plan for the following six months.

    f. Preprints, reprints, and abstracts of all contract-supported work resulted in publication or presentation in the reporting period shall be submitted along with the report.

    NOTE: Semi-annual Technical Progress Reports are not due for periods in which an annual or final report is due.

    NOTE: Electronic copies should be provided as PDF files on CD-ROM, initially. Changes to the electronic medium may be necessary as technology evolves. Any changes require PO approval.

2. Annual Reports. Within 30 days after the anniversary date of the contract, the Contractor shall submit two (2) paper copies and one (1) electronic copy (see semi-annual report for medium) of an Annual Technical Progress Report, as above, comprising one (1) paper copy and the electronic copy to the PO and one (1) paper copy to the CO. Such reports shall detail, document, and summarize the results of the entire contract work for the period covered. These reports shall be in sufficient detail to explain comprehensively the results achieved. Also to be included in the report is a summary of work proposed for the next reporting period. A one-page summary of each ongoing and completed protocol shall be submitted at this time. An annual report will not be required for the period when the final report is due. Preprints and reprints of papers and abstracts not submitted in the semi-annual report shall be submitted. A comprehensive list of publications for the year shall also be submitted.

3. Annual Clinical Research Agenda. Within 30 days of the meeting of the ad hoc group of experts, the Contractor shall submit a research plan outlining the implementation of the studies recommended by the panel. The contractor shall submit (2) paper copies and one electronic copy (PDF files on CD-ROM, see above) of the most recently reviewed and approved Annual Research Agenda, as above, comprising one (1) copy to the PO and one (1) copy to the CO. Such reports shall detail, document and summarize the prioritized research agenda developing strategies and a plan with scientific rationale that identifies the gaps in the existing knowledge or therapeutics status (as recommended by the expert panel) and how the proposed studies will address the gaps.

4. Standard Operating Procedures. Three months after initiation of the contract and annually thereafter, the Contractor shall submit one (1) paper copy and one (1) electronic copy (see above) of the Standard Operating Procedures (SOPs) for the conduct of business by the CASG to the PO for review and approval. The SOPs should include, but are not limited to: methods by which the development, review and implementation of approved protocols will occur, including criteria for evaluation and prioritization; review and approval of publications, abstracts, reports and presentations; reporting of adverse events and serious adverse events; case report form development and review; and Biostatistical unit responsibilities. A comprehensive list of the SOPs that will be required by this contract will be provided to the contractor annually by the PO.

5. Clinical Site Monitoring, Three months after initiation of the contract, and annually thereafter, the Contractor shall submit one(1) paper copy and one (1) electronic copy of a plan for monitoring and evaluating the performance of clinical study sites, including studies conducted at the contract site, and procedures for addressing performance problems to the PO for review and approval.

6. Accrual and Site Registration Report. At specified time points to be determined by the Central Unit and approved by the PO, the Contractor shall submit a report (one (1) paper copy and one (1) electronic copy) for each open clinical study summarizing:

    a. For each clinical site enrolling study participants in open clinical protocols: date of first enrollment, actual accrual to date, summary of all eligible patients per month and to date, and reasons for non-entry of eligible patients.

    b. For each clinical site in the process of registering with the Central Unit and obtaining IRB approval to participate in a specific study: status of each sites documentation and IRB approvals and any anticipated problems with protocol approval/implementation.

    c. Recommendations for modifications in study design, clinical site monitoring, or clinical site training appropriate to improve overall or site-specific accrual, including recommendations for increasing the number of participating clinical sites.

7. List of Responsibilities. The Contractor shall submit to the PO one paper copy (1) and one (1) electronic copy (see above) of a list of responsibilities (LOR) delineating the role of the CASG Central Unit and investigators, industry sponsor(s) (if any), collaborative groups (if any), and NIAID for each study undertaken at least 60 calendar days prior to the expected implementation date for the study for review and approval by the PO.

8. Directory of CASG Investigators. Submit one (1) paper and (1) electronic copy (see above) to the PO and one (1) paper copy to the CO of the semi-annual updates of the Directory of CASG Investigators with complete contact information, including business address, phone number, fax number and email.

9. Final Report. Within 30 calendar days following completion date of the contract, the Contractor shall submit two (2) paper copies and one electronic copy (see above) of a comprehensive Final Report, as above, comprising one (1) paper and one electronic copy to the PO and one (1) paper copy to the CO. This final report shall detail, document, and summarize the results of the entire contract work for the period covered. This report shall be in sufficient detail to explain comprehensively the results achieved. A comprehensive list of publications for the entire contract period shall be included. Preprints and reprints not included in previously submitted reports shall be included.

B. If the Contractor becomes unable to deliver the reports specified hereunder within the period of performance because of unforeseen difficulties, notwithstanding the exercise of good faith and diligent efforts in performance of the work, the Contractor shall give the CO immediate written notice of anticipated delays with reasons therefore.

C. Technical Report Distribution.

Copies of the technical reports and other deliverables shall be submitted as follows:

Type of Report	No. of Copies	Electronic Copy*	Addressee/Distribution	Due Dates
Semi-Annual Progress	1	1	Project Officer (PO) DMID, NIAID, NIH Bethesda, MD 20892-7640	Semi-Annually (Specific dates will be listed in the contract document)
Semi-Annual Progress	1		Contracting Officer (CO) CMB, NIAID, NIH Bethesda, MD 20892-7612	Same as above
Annual Report	1	1	Same as PO above	Within 30 days after the contract anniversary date
Annual Report	1		Same as CO above	Same as above
Clinical Research Agenda	1	1	Same as PO above	Within 30 days after the expert panel meeting annually
Annual Research Agenda	1		Same as CO above	Same as above
Standard Operating Procedures	1	1	Same as PO above	Three months after initiation of the contract and annually thereafter
Clinical Site Monitoring	1	1	Same as PO above	Same as above
Accrual and Site Registration Report	1	1	Same as PO above	To be specified by PO
List of Responsibilities	1	1	Same as PO above	60 days prior to implementation of any study
Directory of CASG Investigators	1	1	Same as PO above	Semi-annually
Directory of CASG Investigators	1	1	Same as PO above	Semi-annually
Final Report	1	1	Same as PO above	Within 30 days of completion of the contract
Final Report	1		Same as CO above	Within 30 days of completion of the contract

PART I - THE SCHEDULE

SECTIONS B - H -- UNIFORM CONTRACT FORMAT - GENERAL

A Sample Uniform Contract Format may be found at the following website:

http://www4.od.nih.gov/ocm/contracts/rfps/sampkt.htm

[Disregard SECTION I and J of this sample. Those SECTIONS have been incorporated as part of this RFP.]

PART II – CONTRACT CLAUSES

SECTION I - CONTRACT CLAUSES

THE FOLLOWING PAGES CONTAIN A LISTING(S) OF GENERAL CLAUSES WHICH WILL BE APPLICABLE TO MOST CONTRACTS RESULTING FROM THIS RFP. HOWEVER, THE ORGANIZATIONAL STRUCTURE OF THE SUCCESSFUL OFFEROR(S) WILL DETERMINE THE SPECIFIC GENERAL CLAUSES LISTING TO BE CONTAINED IN THE CONTRACT(S) AWARDED FROM THIS RFP.

ARTICLE I.1. GENERAL CLAUSES FOR A COST-REIMBURSEMENT RESEARCH AND DEVELOPMENT CONTRACT – FAR 52.252-2, CLAUSES INCORPORATED BY REFERENCE (FEBRUARY 1998)

This contract incorporates the following clauses by reference, with the same force and effect as if they were given in full text. Upon request, the Contracting Officer will make their full text available. Also, the full text of a clause may be accessed electronically at this URL: http://www.arnet.gov/far/.

a. FEDERAL ACQUISITION REGULATION (FAR) (48 CHAPTER 1) CLAUSES

FAR Clause No.	Date	Title
52.202-1	Dec 2001	Definitions
52.203-3	Apr 1984	Gratuities (Over $100,000)
52.203-5	Apr 1984	Covenant Against Contingent Fees (Over $100,000)
52.203-6	Jul 1995	Covenant Against Contingent Fees (Over $100,000)
52.203-7	Jul 1995	Anti-Kickback Procedures (Over $100,000)
52.203-8	Jan 1997	Cancellation, Rescission, and Recovery of Funds for Illegal or Improper Activity (Over $100,000)
52.203-10	Jan 1997	Price or Fee Adjustment for Illegal or Improper Activity (Over $100,000)
52.203-12	Jun 1997	Limitation on Payments to Influence Certain Federal Transactions (Over $100,000)
52.204-4	Aug 2000	Printing/Copying Double-Sided on Recycled Paper (Over $100,000)
52.209-6	Jul 1995	Protecting the Governments Interests When Subcontracting With Contractors Debarred, Suspended, or Proposed for Debarment (Over $25,000)
52.215-2	Jun 1999	Audit and Records - Negotiation (Over $100,000)
52.215-8	Oct 1997	Order of Precedence – Uniform Contract Format
52.215-10	Oct 1997	Price Reduction for Defective Cost or Pricing Data
52.215-12	Oct 1997	Subcontractor Cost or Pricing Data (Over $500,000)
52.215-14	Oct 1997	Integrity of Unit Prices (Over $100,000)
52.215-15	Dec 1998	Pension Adjustments and Asset Reversions
52.215-18	Oct 1997	Reversion or Adjustment of Plans for Post-Retirement Benefits (PRB) Other Than Pensions
52.215-19	Oct 1997	Notification of Ownership Changes
52.215-21	Oct 1997	Requirements for Cost or Pricing Data or Information Other Than Cost or Pricing Data - Modifications
52.216-7	Feb 2002	Allowable Cost and Payment
52.216-8	Mar 1997	Fixed Fee
52.219-8	Oct 2000	Utilization of Small Business Concerns (Over $100,000)

52.219-9	Jan 2002	Small Business Subcontracting Plan (Over $500,000)
52.219-16	Jan 1999	Liquidated Damages - Subcontracting Plan (Over $500,000)
52.222-2	Jul 1990	Payment for Overtime Premium (Over $100,000) (NOTE: The dollar amount in paragraph (a) of this clause is $0 unless otherwise specified in the contract.)
52.222-3	Aug 1996	Convict Labor
52.222-26	Apr 2002	Equal Opportunity
52.222-35	Dec 2001	Equal Opportunity for Special Disabled Veterans, Veterans of the Vietnam Era, and Other Eligible Veterans
52.222-36	Jun 1998	Affirmative Action for Workers with Disabilities
52.222-37	Dec 2001	Employment Reports on Special Disabled Veterans, Veterans of the Vietnam Era, and Other Eligible Veterans
52.223-6	May 2001	Drug-Free Workplace
52.223-14	Oct 2000	Toxic Chemical Release Reporting
52.225-1	May 2002	Buy American Act - Supplies
52.225-13	Jul 2000	Restrictions on Certain Foreign Purchases
52.227-1	Jul 1995	Authorization and Consent, Alternate I (Apr 1984)
52.227-2	Aug 1996	Notice and Assistance Regarding Patent and Copyright Infringement (Over $100,000)
52.227-11	Jun 1997	Patent Rights - Retention by the Contractor (Short Form) (NOTE: In accordance with FAR 27.303 (a) (2), paragraph (f) is modified to include the requirements in FAR 27.303 (a) (2) (i) through (iv). The frequency of reporting in (i) is annual.
52.227-14	Jun 1987	Rights in Data – General
52-232-9	Apr 1984	Limitation on Withholding of Payments
52.232-17	Jun 1996	Interest (Over $100,000)
52.232-20	Apr 1984	Limitation of Cost
52.232-23	Jan 1986	Assignment of Claims
52.232-25	Feb 2002	Prompt Payment
52.232-34	May 1999	Payment by Electronic Funds Transfer--Other Than Central Contractor Registration
52.233-1	Dec 1998	Disputes
52.233-3	Aug 1996	Protest After Award
52.242-1	Apr 1984	Notice of Intent to Disallow Costs
52.242-3	May 2001	Penalties for Unallowable Costs (Over $500,000)
52.242-4	Jan 1997	Certification of Final Indirect Costs

52.242-13	Jul 1995	Bankruptcy (Over $100,000)
52.243-2	Aug 1987	Changes - Cost Reimbursement, Alternate V (Apr 1984)
52.244-2	Aug 1998	Subcontracts, Alternate II (Aug 1998) *If written consent to subcontract is required, the identified subcontracts are listed in ARTICLE B., Advance Understandings.
52.244-5	Dec 1996	Competition in Subcontracting (Over $100,000)
52.245-5	Jan 1986	Government Property (Cost-Reimbursement, Time and Material, or Labor Hour Contract)
52.246-23	Feb 1997	Limitation of Liability (Over $100,000)
52.249-6	Sep 1996	Termination (Cost-Reimbursement)
52.249-14	Apr 1984	Excusable Delays

b. DEPARTMENT OF HEALTH AND HUMAN SERVICES ACQUISITION REGULATION (HHSAR) (48 CFR CHAPTER 3) CLAUSES

HHSAR Clause No.	Date	Title
352.202-1	Jan 2001	Definitions - with Alternate paragraph (h) (Jan 2001)
352.228-7	Dec 1991	Insurance - Liability to Third Persons
352.232-9	Apr 1984	Withholding of Contract Payments
352.233-70	Apr 1984	Litigation and Claims
352.242-71	Apr 1984	Final Decisions on Audit Findings
352.270-5	Apr 1984	Key Personnel
352.270-6	Jul 1991	Publication and Publicity

ARTICLE I.2. AUTHORIZED SUBSTITUTIONS OF CLAUSES

Any authorized substitutions and/or modifications other than the General Clauses which will be based on the type of contract/Contractor will be determined during negotiations.

It is expected that the following clause(s) will be made part of the resultant contract:

ALTERNATE II, (APRIL 1998) of FAR Clause 52.215-2, AUDIT AND RECORDS--NEGOTIATION (JUNE 1999) is added.

FAR Clause 52.232-20, LIMITATION OF COST, is deleted in its entirety and FAR Clause 52.232-22, LIMITATION OF FUNDS (APRIL 1984) is substituted therefor. **[Note: When this contract is fully funded, FAR Clause 52.232-22, LIMITATION OF FUNDS will no longer apply and FAR Clause 52.232-20, LIMITATION OF COST will become applicable.]**

ARTICLE I.3. ADDITIONAL CONTRACT CLAUSES

Additional clauses other than those listed below which are based on the type of contract/Contractor shall be determined during negotiations. Any contract awarded from this solicitation will contain the following:

This contract incorporates the following clauses by reference, (unless otherwise noted), with the same force and effect as if they were given in full text. Upon request, the Contracting Officer will make their full text available.

a. FEDERAL ACQUISITION REGULATION (FAR) (48 CFR CHAPTER 1) CLAUSES

FAR 52.217-9, Option to Extend the Term of the Contract (MARCH 2000).

"(a) The Government may extend the term of this contract by written notice to the Contractor within [INSERT THE PERIOD OF TIME WITHIN WHICH THE CONTRACTING OFFICER MAY EXERCISE THE OPTION] ; provided that the Government gives the Contractor a preliminary written notice of its intent to extend at least days [60 days unless a different number of days is inserted] before the contract expires. The preliminary notice does not commit the Government to an extension."

The total duration of this contract, including the exercise of any options under this clause, shall not exceed June 30, 2009.

FAR 52.219-23, Notice of Price Evaluation Adjustment for Small Disadvantaged Business Concerns (MAY 2001).

"(b) Evaluation adjustment. (1) The Contracting Officer will evaluate offers by adding a factor of ten percent to the price of all offers, except--..."

FAR 52.219-25, Small Disadvantaged Business Participation Program--Disadvantaged Status and Reporting (OCTOBER 1999).

FAR 52.224-1, Privacy Act Notification (APRIL 1984).

FAR 52.224-2, Privacy Act (APRIL 1984).

FAR 52.227-16, Additional Data Requirements (JUNE 1987).

FAR 52.227-17, Rights in Data--Special Works (JUNE 1987).

FAR 52.227-18, Rights in Data--Existing Works (JUNE 1987).

FAR 52.227-19, Commercial Computer Software--Restricted Rights (JUNE 1987).

FAR 52.230-2, Cost Accounting Standards (APRIL 1998).

FAR 52.237-3, Continuity of Services (JANUARY 1991).

b. DEPARTMENT OF HEALTH AND HUMAN SERVICES ACQUISITION REGULATION/PUBLIC HEALTH SERVICE ACQUISITION REGULATION (HHSAR)/(PHSAR) (48 CHAPTER 3) CLAUSES:

HHSAR 352.270-1, Accessibility of Meetings, Conferences and Seminars to Persons with Disabilities (APRIL 1984).

HHSAR 352.270-8, Protection of Human Subjects (JANUARY 2001).

Note: The Office for Human Research Protections (OHRP), Office of the Secretary (OS), Department of Health and Human Services (DHHS) is the office responsible for oversight of the Protection of Human subjects and should replace Office for Protection from Research Risks (OPRR), National Institutes of Health (NIH) wherever it appears in this clause.

c. NATIONAL INSTITUTES OF HEALTH (NIH) RESEARCH CONTRACTING (RC) CLAUSES:

The following clauses are attached and made a part of this contract:

NIH (RC)-7, Procurement of Certain Equipment (APRIL 1984) (OMB Bulletin 81-16).

NIH(RC)-11, Research Patient Care Costs (4/1/84).

ARTICLE I.4. ADDITIONAL FAR CONTRACT CLAUSES INCLUDED IN FULL TEXT

Additional clauses other than those listed below which are based on the type of contract/Contractor shall be determined during negotiations. Any contract awarded from this solicitation will contain the following:

This contract incorporates the following clauses in full text.

FEDERAL ACQUISITION REGULATION (FAR)(48 CFR CHAPTER 1) CLAUSES:

FAR Clause 52.244-6, SUBCONTRACTS FOR COMMERCIAL ITEMS (MAY 2002)

(a) **Definitions**. As used in this clause--

Commercial item, has the meaning contained in the clause at 52.202-1, Definitions.

Subcontract, includes a transfer of commercial items between divisions, subsidiaries, or affiliates of the Contractor or subcontractor at any tier.

(b) To the maximum extent practicable, the Contractor shall incorporate, and require its subcontractors at all tiers to incorporate, commercial items or nondevelopmental items as components of items to be supplied under this contract.

(c) (1) The Contractor shall insert the following clauses in subcontracts for commercial items:

(i) 52.219-8, Utilization of Small Business Concerns (OCT 2000) (15 U.S.C. 637(d)(2) and (3)), in all subcontracts that offer further subcontracting opportunities. If the subcontract (except subcontracts to small business concerns) exceeds $500,000 ($1,000,000 for construction of any public facility), the subcontractor must include 52.219-8 in lower tier subcontracts that offer subcontracting opportunities.
(ii) 52.222-26, Equal Opportunity (APR 2002) (E.O. 11246).
(iii) 52.222-35, Equal Opportunity for Special Disabled Veterans, Veterans of the Vietnam Era, and Other Eligible Veterans (DEC 2001) (38 U.S.C. 4212(a)).
(iv) 52.222-36, Affirmative Action for Workers with Disabilities (JUN 1998) (29 U.S.C. 793).
(v) 52.247-64, Preference for Privately Owned U.S.-Flag Commercial Vessels (JUN 2000) (46 U.S.C. Appx 1241) (flowdown not required for subcontracts awarded beginning May 1, 1996).

(2) While not required, the Contractor may flow down to subcontracts for commercial items a minimal number of additional clauses necessary to satisfy its contractual obligations.

(d) The Contractor shall include the terms of this clause, including this paragraph (d), in subcontracts awarded under this contract.

PART III - LIST OF DOCUMENTS, EXHIBITS AND OTHER ATTACHMENTS

SECTION J - LIST OF ATTACHMENTS

The following Attachments are provided in full text with this Solicitation:

PACKAGING AND DELIVERY OF PROPOSALS (Attached to this listing)

HOW TO PREPARE AN ELECTRONIC PROPOSAL: (Attached to this listing)

PROPOSAL INTENT RESPONSE SHEET SUBMIT ON/BEFORE: October 15, 2002 (Attached to this listing)

[NOTE: Your attention is directed to the "Proposal Intent Response Sheet". If you intend to submit a proposal, you must complete this form and return it to this office via fax or e-mail on or before the date identified above. The receipt of this form is critical as it contains information essential for CMB's coordination of the electronic submission and review of proposals.]

RFP FORMS AND ATTACHMENTS:

THE RFP FORMS/ATTACHMENTS LISTED BELOW ARE AVAILABLE IN A VARIETY OF FORMATS AND MAY BE VIEWED OR DOWNLOADED DIRECTLY FROM THIS SITE:

http://www.niaid.nih.gov/contract/ref.htm

APPLICABLE TO TECHNICAL PROPOSAL (INCLUDE THESE DOCUMENTS/FORMS WITH YOUR TECHNICAL PROPOSAL):

- **Technical Proposal Cover Sheet**
- **Technical Proposal Cost Information**
- **Summary of Related Activities**
- **Optional Form 310, Protection of Human Subjects Assurance Identification/Certification/Declaration** [When applicable, all institutions must have the form reviewed and approved by their Institutional Review Committee.]
- **Government Notice for Handling Proposals**

Targeted/Planned Enrollment Table

APPLICABLE TO BUSINESS PROPOSAL (INCLUDE WITH YOUR BUSINESS PROPOSAL):

- **NIH-2043, Proposal Summary and Data Record**
- **Small Business Subcontracting Plan Format *[if applicable]***
- **Breakdown of Proposed Estimated Cost (plus fee) and Labor Hours**
- **Offeror's Points of Contact**

TO BECOME CONTRACT ATTACHMENTS (INFORMATION ONLY):

Inclusion Enrollment Report

- **NIH(RC)-4: Invoice/Financing Request and Contract Financial Reporting Instructions for NIH Cost-Reimbursement Type Contracts**
- **NIH(RC)-7: Procurement of Certain Equipment, (OMB Bulletin 81-16)**
- **Safety and Health, HHSAR Clause 352.223-70**
- **Privacy Act System of Records**
- **Report of Government Owned, Contractor Held Property**
- **Government Property – Schedule ___**
- **Disclosure of Lobbying Activities, OMB Form LLL**

PACKAGING/DELIVERY/ELECTRONIC SUBMISSION OF THE PROPOSAL

Listed below are delivery instructions for the submission of both PAPER and ELECTRONIC COPIES of your proposal.

PAPER SUBMISSION: The paper copy is the official copy for recording timely receipt of proposals. *You are required to submit one original paper copy of your proposal along with the number of extra copies required below.*

ELECTRONIC SUBMISSION: In addition to the paper submission, you are required to submit your proposal electronically through the CRON (Contracts Review Online) in accordance with the instructions provided below. If you experience difficulty or are unable to transmit, you should submit your proposal on a CD-Rom or ZipDisk by an express delivery service. We can then upload your proposal into the electronic system. You must certify that both the original paper and electronic versions of the proposal are identical.

SUBMISSION OF PROPOSALS BY FACSIMILE IS NOT ACCEPTABLE.

Shipment and marking of paper copies shall be as indicated below:

A. EXTERNAL PACKAGE MARKING:

In addition to the address cited below, mark each package as follows:

"RFP NO. NIH-NIAID-DMID -03-08
TO BE OPENED BY AUTHORIZED GOVERNMENT PERSONNEL ONLY"

B. NUMBER OF COPIES:

The number of copies required of each part of your proposal are as specified below.

Technical Proposal: One (1) unbound signed original and five (5) unbound copies. Ten (10) copies of all material not available electronically (i.e. SOPs, Pertinent Manuals, Nonscannable Figures or Data, and Letters of Collaboration/Intent).

Business Proposal: One (1) unbound signed original and 5 unbound copies.

C. PAPER COPIES and CD-Rom or ZipDisk to:

If Hand Delivery or Express Service	If using U.S. Postal Service
Sharon M. Kraft Contract Specialist Contract Management Branch, DEA NIAID, NIH 6700-B Rockledge Drive, Room 2230 Bethesda, Maryland 20817	Sharon M. Kraft Contract Specialist Contract Management Branch, DEA NIAID, NIH 6700-B Rockledge Drive, Room 2230, MSC 7612 Bethesda, Maryland 20892-7612

NOTE: All material sent to this office by Federal Express should be sent to the Hand Carried Address.

NOTE: The U.S. Postal Service's "Express Mail" does not deliver to the hand delivered (20817 zip code) address. Any package sent to this address via this service will be held at a local post office for pick-up. THE GOVERNMENT IS NOT RESPONSIBLE FOR PICKING UP ANY MAIL AT A LOCAL POST OFFICE. If a proposal is not received at the place, date, and time specified herein, it will be considered a "late proposal," in accordance with HHSAR 352.215-70, Late Proposals and Revisions (NOV 1986).

HOW TO PREPARE AND SUBMIT AN ELECTRONIC PROPOSAL

PAGE LIMITS -- THE TECHNICAL PROPOSAL IS LIMITED TO NOT-TO-EXCEED 200 PAGES [INCLUDING: Appendices, Attachments, Operating Manuals, Non-Scannable Figures or Data, Letters of Intent, etc.]. ANY PORTIONS OF YOUR PROPOSAL NOT AVAILABLE ELECTRONICALLY ARE ALSO CONSIDERED TO BE INCLUDED IN THE TOTAL PAGE LIMITATION. PAGES IN EXCESS OF THIS LIMITATION WILL BE REMOVED FROM THE PROPOSAL AND WILL NOT BE READ OR EVALUATED.

Note that although no page limit has been placed on the Business Proposal, offerors are encouraged to limit its content to only those documents necessary to provide adequate support for the proposed costs.

ELECTRONIC SUBMISSION – To submit a proposal electronically under this RFP, offerors will need to prepare the proposal on a word processor or spreadsheet program (for the business portion) and convert them to Adobe Acrobat Portable Document Format (.pdf). THE TECHNICAL PROPOSAL AND BUSINESS PROPOSAL MUST BE CONTAINED ON SEPARATE FILES which must be identified as either TECHNICAL or BUSINESS and include some recognizable portion of the ORGANIZATION NAME.

Please note that the electronic submission does not replace the requirement to submit a signed, unbound original paper copy of both your Technical and Business Proposal, along with any required unbound duplicate copies. These paper originals should be mailed or hand-delivered to the address provided in this attachment and must be received on/before the closing date and time.

There is no limit to the size (MB) of the two electronic PDF files to be submitted; however, the size of the technical proposal is limited to the page limitation language outlined above. For purposes of assessing compliance with the page count, technical proposals will be viewed using the print function of the Adobe Acrobat Reader, Version 4.0 (or higher).

Formatting Requirements:

- Do not embed sound or video (e.g., MPEG) files into the proposal documents. The evaluation system does not have the capability to read these files.
- Keep graphics embedded in documents as simple as possible. Complex graphics require longer periods for the computers used in the evaluation system to draw, and redraw these figures and scrolling through the document is slowed significantly.
- Type density and size must be 10 to 12 points. If constant spacing is used, there should be no more than 15 cpi, whereas proportional spacing should provide an average of no more than 15 cpi. There must be no more than six lines of text within a vertical inch. Margins must be set to 1 inch around.
- Paper size should not exceed 8-1/2 x 11. Larger paper sizes will be counted as 2 pages.
- Limit colors to 256 colors at 1024 x 768 resolution; avoid color gradients.
- Simplify the color palette used in creating figures.
- Be aware of how large these graphics files become. Large files are discouraged.
- Limit scanned images as much as possible.
- Limit appendices and attachments to relevant technical proposal information (e.g., SOPs, pertinent manuals, non-scannable figures or data, resumes, letters of commitment/intent).

SUBMISSION OF "PROPOSAL INTENT TO RESPOND SHEET":

Upon receipt by the Contracting Officer of the "Proposal Intent Response Sheet", offerors will be provided, via e-mail correspondence, specific electronic access information and electronic proposal transmission instructions. For this reason, it is imperative that all offerors who are intending to submit a proposal in response to this RFP contact the Contract Specialist identified in this RFP and complete and submit the attached "Proposal Intent Response Sheet" by the date provided on that Attachment.

CREATE ADOBE PDF ONLINE -- Adobe will allow you to create 5 documents on a trial for free. If you want to use the site regularly it costs $10/month or $100/year. Please link to the following URL for information:

https://createpdf.adobe.com/index.pl/3847995518.39272?BP=IE

LOG-IN / TRANSMISSION INSTRUCTIONS:

1. Log-in Site: Will be provided by the Contract Specialist after receipt of the "Proposal Intent Response Sheet"
2. Log-in Name: Will be provided by the Contract Specialist.
3. Log-in Password: Will be provided by the Contract Specialist.

4. Procedure -- When your proposal is completed and converted to a PDF file using Adobe Acrobat, it is ready to be transmitted electronically. You must upload separate Technical and Business Proposal Files. It is recommended that proposals be transmitted a few days before the due date so that you will have sufficient time to overcome any transmission difficulties.

- You must have Explorer 3.1 or higher.
- It is essential that you use antiviral software to scan all documents.
- Click on "Sign On" and enter your log-in name and password.
- Click on "Browse" to locate your saved files on your computer.
- Click on "Upload Proposal" after you have located the correct file.
- After a file is uploaded, a link to the file will appear under "Upload Files" at the bottom of the screen. Click on that link to view the uploaded file.
- If you experience difficulty in accessing your documents, please contact the appropriate NIH contracts office immediately.
- If you wish to revise your proposal before the closing date and time, simply log in again and re-post.

USER ACCESS TO THE POSTING SITE WILL BE DENIED AFTER THE RFP CLOSING DATE AND TIME PROVIDED WITH THIS RFP OR ITS MOST RECENT AMENDMENT(S).

PROPOSAL INTENT RESPONSE SHEET

RFP No.: NIH-NIAID-DMID-03-08
RFP Title: "Clinical Trials for Antiviral Therapies"

Please review the attached Request for Proposal. Furnish the information requested below and return this page by **October 15, 2002**. Your expression of intent is not binding but will greatly assist us in planning for proposal evaluation.

Since your proposal will be submitted electronically, please include the name and e-mail of the individual to whom the electronic proposal instructions, login code, and password should be provided.

[ ] DO INTEND TO SUBMIT A PROPOSAL
[ ] DO NOT INTEND TO SUBMIT A PROPOSAL FOR THE FOLLOWING REASONS:

Company/Institution Name (print): _____
Address (print): _____
_____
_____
_____

Project Director's Name (print): _____
Title (print): _____
Signature/Date: _____
Telephone Number and E-mail Address (print clearly):
_____
_____

***Name of individual to whom electronic proposal instructions should be sent:**

Name: _____
Title: _____
E-Mail Address: _____
Telephone Number: _____

Names of Collaborating Institutions and Investigators (include Subcontractors and Consultants) (print):

_____
_____
_____
_____
(Continue list on a separate page if necessary)

RETURN VIA FAX OR E-MAIL TO:
CMB, NIAID, NIH
Room 2230
6700-B Rockledge Drive, MSC 7612
Bethesda, MD 20892-7612
Attn: Sharon M. Kraft
RFP-NIH-NIAID- DMID-03-08
FAX# (301) 402-0972
Email : sk371c@nih.gov

PART IV – REPRESENTATIONS AND INSTRUCTIONS

SECTION K - REPRESENTATIONS, CERTIFICATIONS AND OTHER STATEMENTS OF OFFERORS

Representations, Certifications, and Other Statements of Offerors or Quoters (Negotiated).

1. REPRESENTATIONS AND CERTIFICATIONS

The Representations and Certifications required by this particular acquisition can be accessed electronically from the INTERNET at the following address:

http://rcb.cancer.gov/rcb-internet/forms/rcneg.pdf

If you are unable to access this document electronically, you may request a copy from the Contracting Officer identified on the cover page of this solicitation.

IF YOU INTEND TO SUBMIT A PROPOSAL, YOU MUST COMPLETE THE REPRESENTATIONS AND CERTIFICATIONS AND SUBMIT THEM AS PART OF YOUR BUSINESS PROPOSAL.

SECTION L - INSTRUCTIONS, CONDITIONS, AND NOTICES TO OFFERORS

1. GENERAL INFORMATION

a. **INSTRUCTIONS TO OFFERORS--COMPETITIVE ACQUISITION** [FAR Clause 52.215-1 (May 2001)]

(a) *Definitions*. As used in this provision--

Discussions are negotiations that occur after establishment of the competitive range that may, at the Contracting Officer's discretion, result in the offeror being allowed to revise its proposal.

"*In writing*", "writing", or "*written*" any worded or numbered expression that can be read, reproduced, and later communicated, and includes electronically transmitted and stored information.

"*Proposal modification*" is a change made to a proposal before the solicitation's closing date and time, or made in response to an amendment, or made to correct a mistake at any time before award.

"*Proposal revision*" is a change to a proposal made after the solicitation closing date, at the request of or as allowed by a Contracting Officer as the result of negotiations.

"*Time,*" if stated as a number of days, is calculated using calendar days, unless otherwise specified, and will include Saturdays, Sundays, and legal holidays. However, if the last day falls on a Saturday, Sunday, or legal holiday, then the period shall include the next working day.

(b) *Amendments to solicitations*. If this solicitation is amended, all terms and conditions that are not amended remain unchanged. Offerors shall acknowledge receipt of any amendment to this solicitation by the date and time specified in the amendment(s).

(c) *Submission, modification, revision, and withdrawal of proposals*. (1) Unless other methods (*e.g.*, electronic commerce or facsimile) are permitted in the solicitation, proposals and modifications to proposals shall be submitted in paper media in sealed envelopes or packages (i) addressed to the office specified in the solicitation, and (ii) showing the time and date specified for receipt, the solicitation number, and the name and address of the offeror. Offerors using commercial carriers should ensure that the proposal is marked on the outermost wrapper with the information in paragraphs (c)(1)(i) and (c)(1)(ii) of this provision.

(2) The first page of the proposal must show--

(i) The solicitation number;
(ii) The name, address, and telephone and facsimile numbers of the offeror (and electronic address if available);
(iii) A statement specifying the extent of agreement with all terms, conditions, and provisions included in the solicitation and agreement to furnish any or all items upon which prices are offered at the price set opposite each item;
(iv) Names, titles, and telephone and facsimile numbers (and electronic addresses if available) of persons authorized to negotiate on the offeror's behalf with the Government in connection with this solicitation; and
(v) Name, title, and signature of person authorized to sign the proposal. Proposals signed by an agent shall be accompanied by evidence of that agent's authority, unless that evidence has been previously furnished to the issuing office.

(3) *Submission, modification, revision, and withdrawal of proposals*. (i) Offerors are responsible for submitting proposals, and any modifications or revisions, so as to reach the Government office designated in the solicitation by the time specified in the solicitation. If no time is specified in the solicitation, the time for receipt is 4:30 p.m., local time, for the designated Government office on the date that proposal or revision is due.

(ii) (A) Any proposal, modification, or revision received at the Government office designated in the solicitation after the exact time specified for receipt of offers is "late" and will not be considered unless it

is received before award is made, the Contracting Officer determines that accepting the late offer would not unduly delay the acquisition; and--

(1) If it was transmitted through an electronic commerce method authorized by the solicitation, it was received at the initial point of entry to the Government infrastructure not later than 5:00 p.m. one working day prior to the date specified for receipt of proposals; or

(2) There is acceptable evidence to establish that it was received at the Government installation designated for receipt of offers and was under the Government's control prior to the time set for receipt of offers; or

(3) It is the only proposal received.

(B) However, a late modification of an otherwise successful proposal that makes its terms more favorable to the Government, will be considered at any time it is received and may be accepted.

(iii) Acceptable evidence to establish the time of receipt at the Government installation includes the time/date stamp of that installation on the proposal wrapper, other documentary evidence of receipt maintained by the installation, or oral testimony or statements of Government personnel.

(iv) If an emergency or unanticipated event interrupts normal Government processes so that proposals cannot be received at the office designated for receipt of proposals by the exact time specified in the solicitation, and urgent Government requirements preclude amendment of the solicitation, the time specified for receipt of proposals will be deemed to be extended to the same time of day specified in the solicitation on the first work day on which normal Government processes resume.

(v) Proposals may be withdrawn by written notice received at any time before award. Oral proposals in response to oral solicitations may be withdrawn orally. If the solicitation authorizes facsimile proposals, proposals may be withdrawn via facsimile received at any time before award, subject to the conditions specified in the provision at 52.215-5, Facsimile Proposals. Proposals may be withdrawn in person by an offeror or an authorized representative, if the identity of the person requesting withdrawal is established and the person signs a receipt for the proposal before award.

(4) Unless otherwise specified in the solicitation, the offeror may propose to provide any item or combination of items.

(5) Offerors shall submit proposals in response to this solicitation in English, unless otherwise permitted by the solicitation, and in U.S. dollars, unless the provision at FAR 52.225-17, Evaluation of Foreign Currency Offers, is included in the solicitation.

(6) Offerors may submit modifications to their proposals at any time before the solicitation closing date and time, and may submit modifications in response to an amendment, or to correct a mistake at any time before award.

(7) Offerors may submit revised proposals only if requested or allowed by the Contracting Officer.

(8) Proposals may be withdrawn at any time before award. Withdrawals are effective upon receipt of notice by the Contracting Officer.

(d) *Offer expiration date*. Proposals in response to this solicitation will be valid for the number of days specified on the solicitation cover sheet (unless a different period is proposed by the offeror).

[Note: In accordance with HHSAR 352.215-1, the following paragraph (e) is substituted for the subparagraph (e) of the provision at FAR 52.215-1.]

(e) *Restriction on disclosure and use of data*. (1) The proposal submitted in response to this request may contain data (trade secrets; business data, e.g., commercial information, financial information, and cost and pricing data; and technical data) which the offeror, including its prospective subcontractor(s), does not want used or disclosed for any purpose other than for evaluation of the proposal. The use and disclosure of any data may be so restricted; provided, that the Government determines that the data is not required to be disclosed under the Freedom of Information Act, 5 U.S.C. 552, as amended, and the offeror marks the cover sheet of the proposal with the following legend, specifying the particular portions of the proposal which are to be restricted in accordance with the conditions of the legend. The Government's determination to withhold or disclose a record will be based upon the particular circumstances involving the record in question and whether the record may be exempted from disclosure under the Freedom of Information Act. The legend reads:

Unless disclosure is required by the Freedom of Information Act, 5 U.S.C. 552, as amended, (the Act) as determined by Freedom of Information (FOI) officials of the Department of Health and Human Services, data contained in the portions of this proposal which have been specifically identified by page number, paragraph, etc. by the offeror as containing restricted information shall not be used or disclosed except for evaluation purposes.

The offeror acknowledges that the Department may not be able to withhold a record (data, document, etc.) nor deny access to a record requested pursuant to the Act and that the Department's FOI officials must make that determination. The offeror hereby agrees that the Government is not liable for disclosure if the Department has determined that disclosure is required by the Act.

If a contract is awarded to the offeror as a result of, or in connection with, the submission of this proposal, the Government shall have right to use or disclose the data to the extent provided in the contract. Proposals not resulting in a contract remain subject to the Act.

The offeror also agrees that the Government is not liable for disclosure or use of unmarked data and may use or disclose the data for any purpose, including the release of the information pursuant to requests under the Act. The data subject to this restriction are contained in pages (insert page numbers, paragraph designations, etc. or other identification).

(2) In addition, the offeror should mark each page of data it wishes to restrict with the following statement:

"Use or disclosure of data contained on this page is subject to the restriction on the cover sheet of this proposal or quotation."

(3) Offerors are cautioned that proposals submitted with restrictive legends or statements differing in substance from the above legend may not be considered for award. The Government reserves the right to reject any proposal submitted with a nonconforming legend.

(f) *Contract award*. (1) The Government intends to award a contract or contracts resulting from this solicitation to the responsible offeror(s) whose proposal(s) represents the best value after evaluation in accordance with the factors and subfactors in the solicitation.

(2) The Government may reject any or all proposals if such action is in the Government's interest.

(3) The Government may waive informalities and minor irregularities in proposals received.

(4) The Government intends to evaluate proposals and award a contract without discussions with offerors (except clarifications as described in FAR 15.306(a)). Therefore, the offeror's initial proposal should contain the offeror's best terms from a cost or price and technical standpoint. The Government reserves the right to conduct discussions if the Contracting Officer later determines them to be necessary. If the Contracting Officer determines that the number of proposals that would otherwise be in the competitive range exceeds the number at which an efficient competition can be conducted, the Contracting Officer may limit the number of proposals in the competitive range to the greatest number that will permit an efficient competition among the most highly rated proposals.

(5) The Government reserves the right to make an award on any item for a quantity less than the quantity offered, at the unit cost or prices offered, unless the offeror specifies otherwise in the proposal.

(6) The Government reserves the right to make multiple awards if, after considering the additional administrative costs, it is in the Government's best interest to do so.

(7) Exchanges with offerors after receipt of a proposal do not constitute a rejection or counteroffer by the Government.

(8) The Government may determine that a proposal is unacceptable if the prices proposed are materially unbalanced between line items or subline items. Unbalanced pricing exists when, despite an acceptable total evaluated price, the price of one or more contract line items is significantly overstated or understated as indicated by the application of cost or price analysis techniques. A proposal may be rejected if the Contracting Officer determines that the lack of balance poses an unacceptable risk to the Government.

(9) If a cost realism analysis is performed, cost realism may be considered by the source selection authority in evaluating performance or schedule risk.

(10) A written award or acceptance of proposal mailed or otherwise furnished to the successful offeror within the time specified in the proposal shall result in a binding contract without further action by either party.

(11) The Government may disclose the following information in postaward debriefings to other offerors:

(i) The overall evaluated cost or price and technical rating of the successful offeror;
(ii) The overall ranking of all offerors, when any ranking was developed by the agency during source selection;
(iii) A summary of the rationale for award; and
(iv) For acquisitions of commercial items, the make and model of the item to be delivered by the successful offeror.

(End of Provision)

Alternate I (October 1997). As prescribed in 15.209(a)(1), substitute the following paragraph (f)(4) for paragraph (f)(4) of the basic provision:

(f) (4) The Government intends to evaluate proposals and award a contract after conducting discussions with offerors whose proposals have been determined to be within the competitive range. If the Contracting Officer determines that the number of proposals that would otherwise be in the competitive range exceeds the number at which an efficient competition can be conducted, the Contracting Officer may limit the number of proposals in the competitive range to the greatest number that will permit an efficient competition among the most highly rated proposals. Therefore, the offeror's initial proposal should contain the offeror's best terms from a price and technical standpoint.

b. **NAICS CODE AND SIZE STANDARD**

Note: The following information is to be used by the offeror in preparing its Representations and Certifications (See Section K of this RFP), specifically in completing the provision entitled, SMALL BUSINESS PROGRAM REPRESENTATION, FAR Clause 52.219-1.

(1) The North American Industry Classification System (NAICS) code for this acquisition is 54171.
(2) The small business size standard is 500 employees.

THIS REQUIREMENT IS NOT SET-ASIDE FOR SMALL BUSINESS. However, the Federal Acquisition Regulation (FAR) requires in every solicitation, (except for foreign acquisitions) the inclusion of the North American Industry Classification System (NAICS) Code and corresponding size standard which best describes the nature of the requirement in the solicitation.

c. **NOTICE OF PRICE EVALUATION ADJUSTMENT FOR SMALL DISADVANTAGED BUSINESS CONCERNS**

In accordance with FAR Clause 52.219-23, Notice of Price Evaluation Adjustment for Small Disadvantaged Business Concerns, incorporated in Section I.3., offerors will be evaluated by adding a factor of 10 percent to the price of all offers, except offers from small disadvantaged business concerns that have not waived the adjustment. (Note: A listing

of other offerors who are excepted and will not have this evaluation factor added to their offer may be found in subparagraph (b) of FAR Clause 52.219-23.

A small disadvantaged business concern may elect to waive the adjustment, in which case the factor will be added to its offer for evaluation purposes. The agreements in paragraph (d) of FAR Clause 52.219-23 do not apply to offerors that waive the adjustment.

AN OFFEROR WHO ELECTS TO WAIVE THIS EVALUATION ADJUSTMENT MUST SPECIFICALLY INDICATE WITH A STATEMENT TO THIS EFFECT ON THE COVER PAGE OF ITS BUSINESS PROPOSAL.

d. TYPE OF CONTRACT AND NUMBER OF AWARD(S)

It is anticipated that one award will be made from this solicitation and that the award will be made on/about July 1, 2003.

It is anticipated that the award from this solicitation will be a multiple-year cost reimbursement, completion type contract with a period of performance of approximately seven (7) years, and that incremental funding will be used [see Section L.2.c. Business Proposal Instructions].

e. ESTIMATE OF EFFORT

It is expected that a completion type contract will be awarded as a result of this RFP. To assist you in the preparation of your proposal, the Government considers the effort to be approximately 1,870 labor hours. This information is furnished for the offeror's information only and is not to be considered restrictive for proposal purposes.

Estimated Level of Effort	(% Time per Year)	Total % Time
Principal Investigator	50%	50%
Project Director (Adult Studies)	50%	50%
Project Director (Pediatric Studies)	50%	50%
Clinical Administrators (2)	100%	200%
Study Coordinators (2)	100%	200%
Laboratory Director	50%	50%
Clinical Pharmacologist	25%	25%
Laboratory Scientists (3)	75%	75%
Biostatistics Directors (1)	20%	20%
Biostatistiticians (3)	50%	150%
Program Coordinator (1)	100%	100%
Program Administration (regulatory) (3)	100%	300%
Program Adminstration (operations) (3)	100%	300%
Data analyst	100%	100%
Data Entry Clerks (2)	50%	100%
Database manager	100%	100%

f. COMMITMENT OF PUBLIC FUNDS

The Contracting Officer is the only individual who can legally commit the Government to the expenditure of public funds in connection with the proposed procurement. Any other commitment, either explicit or implied, is invalid.

g. COMMUNICATIONS PRIOR TO CONTRACT AWARD

Offerors shall direct all communications to the attention of the Contract Specialist or Contracting Officer cited on the face page of this RFP. Communications with other officials may compromise the competitiveness of this acquisition and result in cancellation of the requirement.

h. **RELEASE OF INFORMATION**

Contract selection and award information will be disclosed to offerors in accordance with regulations applicable to negotiated acquisition. Prompt written notice will be given to unsuccessful offerors as they are eliminated from the competition, and to all offerors following award.

i. **COMPARATIVE IMPORTANCE OF PROPOSALS**

You are advised that paramount consideration shall be given to the evaluation of technical proposals. All evaluation factors other than cost or price, when combined, are [significantly more important than cost or price/approximately equal to cost or price/significantly less important than cost or price]. The relative importance of the evaluation factors is specified in SECTION M of this solicitation. However, the Government reserves the right to make an award to the best advantage of the Government, cost and other factors considered.

j. **PREPARATION COSTS**

This RFP does not commit the Government to pay for the preparation and submission of a proposal.

k. **SERVICE OF PROTEST** (AUGUST 1996) - FAR 52.233-2

(a) Protests, as defined in section 33.101 of the Federal Acquisition Regulation, that are filed directly with an agency, and copies of any protests that are filed with the General Accounting Office (GAO), shall be served on the Contracting Officer (addressed as follows) by obtaining written and dated acknowledgment of receipt from:

Brenda J. Velez
Contracting Officer
Contract Management Branch, DEA
National Institute of Allergy and Infectious Diseases
6700-B Rockledge Drive, Room 2230, MSC 7612
BETHESDA MD 20892-7612

(b) The copy of any protest shall be received in the office designated above within one day of filing a protest with the GAO.

(End of Provision)

l. **LATE PROPOSALS AND REVISIONS**, HHSAR 352.215-70

Notwithstanding the procedures contained in FAR 52.215-1(c)(3) of the provision of this solicitation entitled Instructions to Offerors—Competitive Acquisition, a proposal received after the date specified for receipt may be considered if it offers significant cost or technical advantages to the Government; and it was received before proposals were distributed for evaluation, or within five calendar days after the exact time specified for receipt, whichever is earlier.

(End of provision)

USE OF INTERNET WEB SITE ADDRESSES (URLs) IN PROPOSALS

Unless otherwise specified or required in NIAID solicitations, internet Web Site addresses (URLs) may not be used to provide information necessary to the conduct of the review of the proposal. Direct access to an internet site by a Reviewer who is examining and reviewing the proposal on behalf of the NIAID could compromise their anonymity during the review process. If a URL contains information pertinent to the proposal content, the offeror must provide access to the website via a temporary website portal which allow reviewers the capability to view and interact with the site.

The proposal must clearly identify the URLs to be accessed and the procedure for accessing the temporary website portal. Access must not require the identity of the individual.

2. INSTRUCTIONS TO OFFERORS

a. GENERAL INSTRUCTIONS

INTRODUCTION

The following instructions will establish the acceptable minimum requirements for the format and contents of proposals. Special attention is directed to the requirements for technical and business proposals to be submitted in accordance with these instructions.

(1) **Contract Type and General Clauses**

It is contemplated that a [cost-reimbursement completion type contract will be awarded. (See General Information) Any resultant contract shall include the clauses applicable to the selected offeror's organization and type of contract awarded as required by Public Law, Executive Order, or acquisition regulations in effect at the time of execution of the proposed contract.

(2) **Authorized Official and Submission of Proposal**

The proposal must be signed by an official authorized to bind your organization and must stipulate that it is predicated upon all the terms and conditions of this RFP. Your proposal shall be submitted in the number of copies, to the addressees, and marked as indicated in the Attachment entitled, PACKAGING AND DELIVERY OF PROPOSAL, Part III, Section J hereof. Proposals will be typewritten, paginated, reproduced on letter size paper and will be legible in all required copies. To expedite the proposal evaluation, all documents required for responding to the RFP should be placed in the following order:

I. COVER PAGE

Include RFP title, number, name of organization, identification of the proposal part, and indicate whether the proposal is an original or a copy.

II. TECHNICAL PROPOSAL

It is recommended that the technical proposal consist of a cover page, a table of contents, and the information requested in the Technical Proposal Instructions and as specified in SECTION J, List of Attachments.

III. BUSINESS PROPOSAL

It is recommended that the business proposal consist of a cover page, a table of contents, and the information requested in the Business Proposal Instructions and as specified in SECTION J, List of Attachments.

(3) **Proposal Summary and Data Record (NIH-2043)**

The Offeror must complete the Form NIH-2043, attached, with particular attention to the length of time the proposal is firm and the designation of those personnel authorized to conduct negotiations. (See Section J, Attachment entitled, PROPOSAL SUMMARY AND DATA RECORD).

(4) **Separation of Technical and Business Proposals**

The proposal must be prepared in two parts: a "Technical Proposal" and a "Business Proposal." Each of the parts shall be separate and complete in itself so that evaluation of one may be accomplished independently of, and concurrently with, evaluation of the other. The technical proposal must include direct cost and resources information, such as labor-hours and categories and applicable rates, materials, subcontracts, travel, etc., and associated costs so that the offeror's understanding of the project may be evaluated (See Attachment entitled, TECHNICAL PROPOSAL COST INFORMATION/SUMMARY OF LABOR AND DIRECT COSTS).) However, the technical proposal should **not** include pricing data relating to individual salary information, indirect cost rates or

amounts, fee amounts (if any)., and total costs. The technical proposal should disclose your technical approach in as much detail as possible, including, but not limited to, the requirements of the technical proposal instructions.

(5) **Alternate Proposals**

You may, at your discretion, submit alternate proposals, or proposals which deviate from the requirements; provided, that you also submit a proposal for performance of the work as specified in the statement of work. Such proposals may be considered if overall performance would be improved or not compromised and if they are in the best interests of the Government. Alternative proposals, or deviations from any requirements of this RFP, shall be clearly identified.

(6) **Evaluation of Proposals**

The Government will evaluate technical proposals in accordance with the criteria set forth in PART IV, SECTION M of this RFP.

(7) **Potential Award Without Discussions**

The Government reserves the right to award a contract without discussions if the Contracting Officer determines that the initial prices are fair and reasonable and that discussions are not necessary.

(8) **Use of the Metric System of Measurement**

It is the policy of the Department of Health and Human Services to support the Federal transition to the metric system and to use the metric system of measurement in all procurements, grants, and other business related activities unless such use is impracticable or is likely to cause significant inefficiencies.

The offeror is encouraged to prepare their proposal using either "Hard Metric," "Soft Metric," or "Dual Systems" of measurement. The following definitions are provided for your information:

Hard Metric - The replacement of a standard inch-pound size with an accepted metric size for a particular purpose. An example of size substitution might be: selling or packaging liquids by the liter instead of by the pint or quart (as for soft drinks), or instead of by the gallon (as for gasoline).

Soft Metric - The result of a mathematical conversion of inch-pound measurements to metric equivalents for a particular purpose. The physical characteristics are not changed.

Dual Systems - The use of both inch-pound and metric systems. For example, an item is designed, produced, and described in inch-pound values with soft metric values also shown for information or comparison purposes.

(9) **Human Subjects**

IMPORTANT NOTE TO OFFERORS: The following 6 paragraphs [(9) through (14)] shall be addressed in a SEPARATE SECTION of the Technical Proposal entitled, "HUMAN SUBJECTS."

The following notice is applicable when contract performance is expected to involve risk to human subjects:

Notice to Offerors of Requirements of 45 CFR Part 46, Protection of Human Subjects (JANUARY 2001)

a) Copies of the Department of Health and Human Services (Department) regulations for the protection of human subjects, 45 CFR Part 46, are available from the Office of Protection from Research Risks (OPRR), National Institutes of Health (NIH), Bethesda, Maryland 20892*. The regulations provide a systematic means, based on established ethical principles, to safeguard the rights and welfare of individuals who participate as subjects in research activities supported or conducted by the Department.

b) The regulations define a human subject as a living individual about whom an investigator (whether professional or student) conducting research obtains data through intervention or interaction with the individual, or identifiable private information. The regulations extend to the use of human organs, tissue and body fluids from individually identifiable human subjects as well as to graphic, written or recorded information derived from individually identifiable human subjects. The use of autopsy materials is governed by applicable State and local law and is not directly regulated by 45 CFR, Part 46.

c) Activities in which the only involvement of human subjects will be in one or more of the categories set forth in 45 CFR 46.101(b)(1-6) are exempt from coverage.

d) Inappropriate designations of the noninvolvement of human subjects or of exempt categories of research in a project may result in delays in the review of a proposal. The National Institutes of Health will make a final determination of whether the proposed activities are covered by the regulations or are in an exempt category, based on the information provided in the proposal. In doubtful cases, prior consideration with OPRR*, (telephone: 301-496-7014*), is recommended.

e) In accordance with 45 CFR, Part 46, prospective Contractors being considered for award shall be required to file with OPRR* an acceptable Assurance of Compliance with the regulations, specifying review procedures and assigning responsibilities for the protection of human subjects. The initial and continuing review of a research project by an institutional review board shall assure that the rights and welfare of the human subjects involved are adequately protected, that the risks to the subjects are reasonable in relation to the potential benefits, if any, to the subjects and the importance of the knowledge to be gained, and that informed consent will be obtained by methods that are adequate and appropriate. Prospective Contractors proposing research that involves human subjects shall be contacted by OPRR* and given detailed instructions for establishing an institutional review board and filing an Assurance of Compliance.

f) It is recommended that OPRR* be consulted for advice or guidance concerning either regulatory requirements or ethical issues pertaining to research involving human subjects. (End of Provision)

*Note: The Office for Human Research Protections (OHRP), Office of the Secretary (OS), Department of Health and Human Services (DHHS) is the office responsible for oversight of the Protection of Human subjects and should replace Office for Protection from Research Risks (OPRR), National Institutes of Health (NIH) wherever it appears in this provision. The phone number to reach this office is 301-496-7014. For more information, the OHRP website may be accessed at http://ohrp.osophs.dhhs.gov/ Copies of the DHHS Regulations for the Protection of Human Subjects, 45 CFR Part 46, are also available on line at http://www.access.gpo.gov/nara/cfr/waisidx_01/45cfr46_01.html.

(10) **Instructions to Offerors Regarding Protection of Human Subjects**

Offerors must address the following human subjects protections issues if this contract will be for research involving human subjects (note: under each of the following points below, the offeror should indicate whether the information provided relates to the primary research site, or to a collaborating performance site(s), or to all sites:

(a) Risks to the subjects

Human Subjects Involvement and Characteristics:

- Describe the proposed involvement of human subjects in response to the solicitation.

- Describe the characteristics of the subject population, including their anticipated number, age range, and health status.

- Identify the criteria for inclusion or exclusion of any subpopulation. Explain the rationale for the involvement of special classes of subjects, such as fetuses, pregnant women, children, prisoners, institutionalized individuals, or others who are likely to be vulnerable populations.

Sources of Materials:

– Identify the sources of research material obtained from individually identifiable living human subjects in the form of specimens, records, or data. Indicate whether the material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records, or data.

Potential Risks:

- Describe the potential risks to subjects (physical, psychological, social, legal, or other) and assess their likelihood and seriousness to the subjects.

- Describe alternative treatments and procedures, including the risks and benefits of the alternative treatments and procedures, to participants in the proposed research, where appropriate.

(b) Adequacy of Protection Against Risks

Recruitment and Informed Consent:

- Describe plans for the recruitment of subjects and the procedures for obtaining informed consent. Include a description of the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent. The informed consent document for the contractor and any collaborating sites should be submitted only if requested elsewhere in the solicitation. Be aware that an IRB-approved informed consent document for the contractor and any participating collaborative sites must be provided to the Government prior to patient accrual or participant enrollment.

Protection Against Risk:

- Describe the procedures for protecting against or minimizing potential risks, including risks to confidentiality, and assess their likely effectiveness.

- Discuss provisions for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects where appropriate.

- In studies that involve interventions, describe the provisions for data and safety monitoring of the research to ensure the safety of subjects.

(c) Potential Benefits of the Proposed Research to the Subjects and Others

- Discuss the potential benefits of the research to the subjects and others.

- Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and others.

- Describe treatments and procedures that are alternatives to those provided to the participants by the proposed research, where appropriate.

(d) Importance of the Knowledge to be Gained

- Discuss the importance of the knowledge gained or to be gained as a result of the proposed research.

- Discuss why the risks to subjects are reasonable in relation to the importance of the knowledge that may reasonably be expected to result.

Note: If a test article (investigational new drug, device, or biologic) is involved, name the test article and state whether the 30-day interval between submission of offeror's certification to the Food and Drug Administration (FDA) and its response has elapsed or has been waived and/or whether the FDA has withheld or restricted use of the test article.

Collaborating Site(s)

When research involving human subjects will take place at collaborating site(s) or other performance site(s), the offeror must provide in this section of its proposal a list of the collaborating sites and their assurance numbers. Further, if you are awarded a contract, you must obtain in writing, and keep on file, an assurance from each site that the previous points have been adequately addressed at a level of attention that is at least as high as that documented at your organization. Site(s) added after an award is made must also adhere to the above requirements.

(11) **Required Education in the Protection of Human Research Participants**

NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for contracts for research involving human subjects. This policy announcement is found in the NIH Guide for Grants and Contracts Announcement dated June 5, 2000 at the following website: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html. Offerors should review the policy announcement prior to submission of their offers. The following is a summary of the Policy Announcement:

For any solicitation for research involving human subjects, the offeror shall provide in its technical proposal the following information: (1) a list of the names of the principal investigator and any other individuals proposed under the contract who are responsible for the design and/or conduct of the research; (2) the title of the education program completed (or to be completed prior to the award of the contract) for each named personnel; (3) a one sentence description of the program(s) listed in (2) above. This requirement extends to investigators and all individuals responsible for the design and/or conduct of the research who are working as subcontractors or consultants under the contract.

Curricula that are readily available and meet the educational requirement include the NIH on-line tutorial, titled "Protection of Human Research Subjects: Computer-Based Training for Researchers," available at http://ohsr.od.nih.gov/cbt/. You may download the information at this site at no cost and modify it, if desired. In addition, the University of Rochester has made its training program available for individual investigators. Completion of this program will also satisfy the educational requirement. The University of Rochester manual can be obtained through Centerwatch, Inc. at http://www.centerwatch.com/order/pubs_profs_protect.html. If an institution already has developed educational programs on the protection of research participants, completion of these programs also will satisfy the educational requirement.

In addition, prior to the substitution of the principal investigator or any other individuals responsible for the design and/or conduct of the research under the contract, the contractor shall provide the contracting officer with the title of the education program and a one sentence description of the program that the replacement has completed.

(12) **Inclusion of Women and Minorities in Research Involving Human Subjects**

It is NIH policy that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects involving human subjects, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. The Director, NIH, may determine that exclusion under other circumstances is acceptable, upon the recommendation of an Institute/Center Director, based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43), ***and applies to research subjects of all ages***.

All investigators proposing research involving human subjects should read the UPDATED "NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, Amended October 2001," published in the NIH Guide for Grants and Contracts on October 9, 2001 at the following web site:

http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm

These guidelines contain a definition of **clinical research** adopted in June 2001, as: "(1) Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this

definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, and (d) development of new technologies; (2) Epidemiologic and behavioral studies; and (3) Outcomes research and health services research" (http://www.nih.gov/news/crp/97report/execsum.htm).

Information Required for ALL Clinical Research Proposals

This solicitation contains a review criterion addressing the adequacy of: (1) the offeror's plans for inclusion of women and minorities in the research proposed; or (2) the offeror's justification(s) for exclusion of one or both groups from the research proposed.

Provide information on the composition of the proposed study population in terms of sex/gender and racial/ethnic groups and provide a rationale for selection of such subjects in response to the requirements of the solicitation. The description may include (but is not limited to) information on the population characteristics of the disease or condition being studied in the planned research, and/or described in the statement of work, national and local demography, knowledge of the racial/ethnic/cultural characteristics of the population, prior experience and collaborations in recruitment and retention of the populations and subpopulations to be studied, and the plans, arrangements and letters of commitment from relevant community groups and organizations for the planned research.

The proposal must include the following information:

- A description of the subject selection criteria
- The proposed dates of enrollment (beginning and end)
- A description of the proposed outreach programs for recruiting women and minorities as subjects
- A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group
- The proposed sample composition using the "Targeted/Planned Enrollment Table"(see Section J, Attachments)

NOTE 1: For all proposals, use the ethnic and racial categories and complete the "Targeted/Planned Enrollment Table in accordance with the Office of Management and Budget (OMB) Directive No. 15, which may be found at: http://www.whitehouse.gov/OMB/fedreg/ombdir15.html

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NOTE 2: If this is an Indefinite Delivery, Indefinite Quantity (IDIQ) or Requirements contract as defined in FAR 16.5, the proposal should describe in general terms how it will comply with each bulleted item above for each task order. When the Government issues a task order request for proposal, each of the bulleted information items must be fully and specifically addressed in the proposal.

Standards for Collecting Data. When you, as a contractor, are planning data collection items on race and ethnicity, you shall use, at a minimum, the categories identified in OMB Directive No. 15. The collection of greater detail is encouraged. However, you should design any additional, more detailed items so that they can be aggregated into these required categories. Self-reporting or self-identification using two separate questions is the preferred method for collecting data on race and ethnicity. When you collect race and ethnicity separately, you must collect ethnicity first. You shall offer respondents the option of selecting one or more racial designations. When you collect data on race and ethnicity separately, you shall also make provisions to report the number of respondents in each racial category who are Hispanic or Latino. When you present aggregate data, you shall provide the number of respondents who selected only one category, for each of the five racial categories. If you collapse data on multiple responses, you shall make available, at a minimum, the total number of respondents reporting "more than one race." Federal agencies shall not present data on detailed categories if doing so would compromise data quality or confidentiality standards.

In addition to the above requirements, solicitations for **NIH defined Phase III clinical trials**[1] require that*:* a) all proposals and/or protocols provide a description of plans to conduct analyses, as appropriate, to detect significant differences in intervention effect (see NIH Guide:

[1]See NIH Guide http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm, for the Definition of an "NIH-Defined Phase III clinical trial.

http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm, Definitions - Significant Difference),

by sex/gender, racial/ethnic groups, and relevant subpopulations, if applicable; and b) all contractors to report annually cumulative subject accrual, and progress in conducting analyses for sex/gender and race/ethnicity differences.

Offerors may obtain copies of the Updated Guidelines from the sources above or from the contact person listed in the solicitation.

Also, the proposal must include one of the following plans:

- Plans to conduct valid analysis to detect significant differences in intervention effect among sex/gender and/or racial/ethnic subgroups when prior studies strongly support these significant differences among subgroups, OR

- Plans to include and analyze sex/gender and/or racial/ethnic subgroups when prior studies strongly support no significant differences in intervention effect between subgroups, OR

- Plans to conduct valid analyses of the intervention effect in sex/gender and/or racial/ethnic subgroups (without requiring high statistical power for each subgroup) when the prior studies neither support nor negate significant differences in intervention effect between subgroups.

Use the form in Section J, Attachments, entitled, "Targeted/Planned Enrollment Table," when preparing your response to the solicitation requirements for inclusion of women and minorities.

Unless otherwise specified in this solicitation, the Government has determined that the work required by this solicitation does not involve a sex/gender specific study or a single or limited number of minority population groups. Therefore, the NIH believes that the inclusion of women and minority populations is appropriate for this project. (See Section M of this RFP for more information about evaluation factors for award.)

Use the format for the Annual Technical Progress Report for Clinical Research Study Populations (See Section J - List of Documents, Exhibits and Other Attachments of the RFP) entitled, "Inclusion Enrollment Report," for reporting in the resultant contract.

(13) **Inclusion of Children in Research Involving Human Subjects**

It is NIH policy that children (defined below) must be included in all human subjects research, including, but not limited to, clinical trials, conducted under a contract funded by the NIH, unless there are *clear and compelling* reasons not to include them. **(See examples of Justifications for Exclusion of Children below).** For the purposes of this policy, contracts involving human subjects include categories that would otherwise be exempt from the DHHS Policy for Protection of Human Research Subjects (sections 101(b) and 401(b) of 45 CFR 46), such as surveys, evaluation of educational interventions, and studies of existing data or specimens that should include children as participants. This policy applies to both domestic and foreign research contracts.

For purposes of this policy, a child is defined as an individual under the age of 21 years.

All offerors proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects" which was published in the NIH Guide for Grants and Contracts on March 6, 1998 and is available at the following URL address:

http://www.nih.gov/grants/guide/notice-files/not98-024.html

Offerors also may obtain copies from the contact person listed in the RFP.

Inclusion of children as participants in research must be in compliance with all applicable subparts of 45 CFR 46 as well as other pertinent laws and regulations whether or not such research is otherwise exempted from 45 CFR 46. Therefore, any proposals must include a description of plans for including children, unless the offeror presents clear and convincing justification for an exclusion. The “Human Subjects” section of your technical proposal should provide either a description of the plans to include children and a rationale for selecting or excluding a specific age

range of child, or an explanation of the reason(s) for excluding children as participants in the research. This solicitation contains a review criterion addressing the adequacy of: (1) the plans for including children as appropriate for the scientific goals of the research; and/or (2) the justification of exclusion of children or exclusion of a specific age range of children.

When children are included, the plan also must include a description of: (1) the expertise of the investigative team for dealing with children at the ages included; (2) the appropriateness of the available facilities to accommodate the children; and, (3) the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose/objective of the solicitation.

Justifications for Exclusion of Children

It is expected that children will be included in all research involving human subjects unless one or more of the following exclusionary circumstances can be fully justified:

- The objective of the solicitation is not relevant to children.

  - There are laws or regulations barring the inclusion of children in the research to be conducted under the solicitation.

  - The knowledge being sought in the research is already available for children or will be obtained from another ongoing study, and an additional study will be redundant. You should provide documentation of other studies justifying the exclusion.

  - A separate, age-specific study in children is warranted and preferable. Examples include:

- The relative rarity of the condition in children, as compared with adults (in that extraordinary effort would be needed to include children); or
- The number of children is limited because the majority are already accessed by a nationwide pediatric disease research network; or
- Issues of study design preclude direct applicability of hypotheses and/or interventions to both adults and children (including different cognitive, developmental, or disease stages of different age-related metabolic processes); or
- Insufficient data are available in adults to judge potential risk in children (in which case one of the research objectives could be to obtain sufficient adult data to make this judgment). While children usually should not be the initial group to be involved in research studies, in some instances, the nature and seriousness of the illness may warrant their participation earlier based on careful risk and benefit analysis; or
- Study designs aimed at collecting additional data on pre-enrolled adult study subjects (e.g., longitudinal follow-up studies that did not include data on children);
- Other special cases justified by the offeror and found acceptable to the review group and the Institute Director

Definition of a Child

For the purpose of this solicitation, a child is defined as an individual under the age of 21 years.

The definition of child described above will pertain to this solicitation (notwithstanding the FDA definition of a child as an individual from infancy to 16 years of age, and varying definitions employed by some states). Generally, State laws define what constitutes a "child," and such definitions dictate whether or not a person can legally consent to participate in a research study. However, State laws vary, and many do not address when a child can consent to participate in research. Federal Regulations (45 CFR 46, subpart D, Sec.401-409) address DHHS protections for children who participate in research, and rely on State definitions of "child" for consent purposes. Consequently, the children included in this policy (persons under the age of 21) may differ in the age at which their own consent is required and sufficient to participate in research under State law. For example, some states consider a person age 18 to be an adult and therefore one who can provide consent without parental permission.

(14) **Data and Safety Monitoring in Clinical Trials**

All offerors are directed to the full text of the NIH Policies regarding Data and Safety Monitoring and Reporting of Adverse Events that are found in the NIH Guide for Grants and Contracts Announcements at the following web sites:

http://grants.nih.gov/grants/guide/notice-files/not98-084.html
http://grants.nih.gov/grants/guide/notice-files/not99-107.html
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html

All offerors receiving an award under this solicitation must comply with the NIH Policy cited in these NIH Announcements and any other data and safety monitoring requirements found elsewhere in this solicitation.

The following is a brief summary of the Data and Safety Monitoring and Adverse Event Reporting Requirements:

Data and Safety Monitoring is required for every clinical trial. Monitoring must be performed on a regular basis and the conclusions of the monitoring reported to the Project Officer.

The type of data and safety monitoring required will vary based on the type of clinical trial and the potential risks, complexity and nature of the trial. A plan for data and safety monitoring is required for all clinical trials. A general description of a monitoring plan establishes the overall framework for data and safety monitoring. It should describe the entity that will be responsible for the monitoring, and the policies and procedures for adverse event reporting. Phase III clinical trials generally require the establishment of a Data Safety Monitoring Board (DSMB). The establishment of a DSMB is optional for Phase I and Phase II clinical trials.

The DSMB/Plan is established at the time the protocol is developed and must be approved by both the Institutional Review Board (IRB) and the Government and in place before the trial begins. If the protocol will be developed under the contract awarded from this solicitation, a general description of the data and safety monitoring plan must be submitted as part of the proposal and will be reviewed by the scientific review group (Technical Evaluation Panel, (TEP)) convened to evaluate the proposal. If the protocol is developed and is included as part of the submitted proposal, a complete and specific data and safety monitoring plan must be submitted as part of the proposal.

Monitoring Plans, at a minimum, must include the prompt reporting of adverse events to the IRB, the NIH Office of Biotechnology Activities (OBA), and the Food and Drug Administration (FDA). Also, in the plan you should describe the frequency of reporting of the conclusions of the monitoring activities. The overall elements of each plan may vary depending on the size and complexity of the trial. The NIH Policy for Data and Safety Monitoring at http://grants.nih.gov/grants/guide/notice-files/not98-084.html describes examples of monitoring activities to be considered.

The frequency of monitoring will depend upon potential risks, complexity, and the nature of the trial; therefore a number of options for monitoring trials are available. These can include, but are not limited to, monitoring by a:

- Principal Investigator (required)
- Independent individual /Safety Officer
- Designated medical monitor
- Internal Committee or Board with explicit guidelines
- Data and Safety Monitoring Board (DSMB - required for multisite trials)
- Institutional Review Board (IRB - required)

For multi-site Phase I and Phase II trials, a central reporting entity that will be responsible for preparing timely summary reports of adverse events for distribution among sites and IRBs should be considered.

Organizations with a large number of clinical trials may develop standard monitoring plans for Phase I and Phase II trials. In this case, such organizations may include the IRB-approved monitoring plan as part of the proposal submission.

(15) **Obtaining and Disseminating Biomedical Research Resources**

As a public sponsor of biomedical research, the National Institutes of Health (NIH) has a dual interest in accelerating scientific discovery and facilitating product development. Intellectual property restrictions can stifle the broad dissemination of new discoveries and limit future avenues of research and product development. At the same time, reasonable restrictions on the dissemination of research tools are sometimes necessary to protect legitimate proprietary interests and to preserve incentives for commercial development. To assist NIH contractors achieve an appropriate balance, the NIH has provided guidance in the form of a two-part document, consisting of Principles setting forth the fundamental concepts and Guidelines that provide specific information to patent and license professionals and sponsored research administrators for implementation.

The purpose of these Principles and Guidelines is to assist NIH funding recipients in determining: 1) Reasonable terms and conditions for making NIH-funded research resources available to scientists in other institutions in the public and private sectors (disseminating research tools); and 2) Restrictions to accept as a conditions of receiving access to research tools for use in NIH-funded research (acquiring research tools). The intent is to help recipients ensure that the conditions they impose and accept on the transfer of research tools will facilitate further biomedical research, consistent with the requirements of the Bayh-Dole Act and NIH funding policy.

This policy, entitled, "Sharing Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Research Grants and Contracts," (Federal Register Notice, December 23, 1999 [64 FR 72090] will be included in any contract awarded from this solicitation. It can be found at the following website: http://ott.od.nih.gov/NewPages/64FR72090.pdf.

(16) **Privacy Act (Treatment of Proposal Information)**

The Privacy Act of 1974 (P.L. 93-579) requires that a Federal agency advise each individual whom it asks to supply information, the authority which authorizes the solicitation, whether disclosure is voluntary or mandatory, the principal purpose or purposes for which the information is intended to be used, the uses outside the agency which may be made of the information, and the effects on the individual, if any, of not providing all or any part of the requested information.

The NIH is requesting the information called for in this RFP pursuant to the authority provided by Sec. 301(a)(7) of the Public Health Service Act, as amended, and P.L. 92-218, as amended.

Providing the information requested is entirely voluntary. The collection of this information is for the purpose of conducting an accurate, fair, and adequate review prior to a discussion as to whether to award a contract.

Failure to provide any or all of the requested information may result in a less than adequate review.

In addition, the Privacy Act of 1974 (P.L. 93-579, Section 7) requires that the following information be provided when individuals are requested to disclose their social security number.

Provision of the social security number is voluntary. Social security numbers are requested for the purpose of accurate and efficient identification, referral, review and management of NIH contracting programs. Authority for requesting this information is provided by Section 301 and Title IV of the PHS Act, as amended.

The information provided by you may be routinely disclosed for the following purposes:

- to the cognizant audit agency and the General Accounting Office for auditing.
- to the Department of Justice as required for litigation.
- to respond to congressional inquiries.
- to qualified experts, not within the definition of Department employees, for opinions as a part of the review process.

(17) **Selection of Offerors**

a) The acceptability of the [scientific and] technical portion of each [research] contract proposal will be evaluated by a technical review committee. The committee will evaluate each proposal in strict conformity with the evaluation criteria of the RFP, utilizing point scores and written critiques. The committee may suggest that the Contracting Officer request clarifying information from an offeror.

b) The business portion of each contract proposal will be subjected to a cost and price analysis, management analysis, etc.

c) If award will be made without conducting discussions, offerors may be given the opportunity to clarify certain aspects of their proposal (e.g., the relevance of an offeror's past performance information and adverse past performance information to which the offeror has not previously had an opportunity to respond) or to resolve minor or clerical errors.

d) If the Government intends to conduct discussions prior to awarding a contract-

(1) Communications will be held with offerors whose past performance information is the determining factor preventing them from being placed within the competitive range. Such communications shall address adverse past performance information to which an offeror has not had a prior opportunity to respond. Also, communications may be held with any other offerors whose exclusion from, or inclusion in, the competitive range is uncertain.

Such communications shall not be used to cure proposal deficiencies or omissions that alter the technical or cost elements of the proposal, and/or otherwise revise the proposal, but may be considered in rating proposals for the purpose of establishing the competitive range.

(2) The Contracting Officer will, in concert with program staff, decide which proposals are in the competitive range. The competitive range will be comprised of all of the most highly rated proposals. Oral or written discussions will be conducted with all offerors in the competitive range.

While it is this Institute's policy to conduct discussions with all offerors in the competitive range, the Institute reserves the right, in special circumstances, to limit the number of proposals included in the competitive range to the greatest number that will permit an efficient competition. All aspects of the proposals are subject to discussions, including cost, technical approach, past performance, and contractual terms and conditions. At the conclusion of discussions, each offeror still in the competitive range shall be given an opportunity to submit a written Final Proposal Revision (FPR) with the reservation of the right to conduct finalization of details with the selected sources in accordance with HHSAR 315.370.

e) The process described in FAR 15.101-1 will be employed, which permits the Government to make tradeoffs among cost or price and non-cost factors and to consider award to other than the lowest price offeror or other than the highest technically rated offeror. This process will take into consideration the results of the technical evaluation, the past performance evaluation (if applicable) and the cost analysis.

f) The Institute reserves the right to make a single award, multiple awards, or no award at all to the RFP. In addition, the RFP may be amended or canceled as necessary to meet the Institute's requirements. Synopses of awards exceeding $25,000 will be published in the Commerce Business Daily and FedBizOpps.

(18) **Small Business Subcontracting Plan**

If the proposed contract exceeds a total estimated cost of $500,000 for the entire period of performance, the offeror shall be required to submit an acceptable subcontracting plan in accordance with the terms of the clause entitled "Small Business Subcontracting Plan," FAR Clause No. 52.219-9, incorporated herein by reference in the Solicitation, Attachment _ to this RFP is an example of such a plan.

a) THIS PROVISION DOES NOT APPLY TO SMALL BUSINESS CONCERNS.

b) The term "subcontract" means any agreement (other than one involving an employer-employee relationship) entered into by a Federal Government prime Contractor or subcontractor calling for supplies or services

required for the performance of the original contract or subcontract. This includes, but is not limited to, agreements/purchase orders for supplies and services such as equipment purchase, copying services, and travel services.

c) The offeror understands that:

(1) No contract will be awarded unless and until an acceptable plan is negotiated with the Contracting Officer which plan will be incorporated into the contract, as a material part thereof.

(2) An acceptable plan must, in the determination of the Contracting Officer, provide the maximum practicable opportunity for Small Businesses, Small Disadvantaged Businesses, Women-Owned Small businesses, HubZone Small Businesses, Veteran-Owned Small Businesses, and Service Disabled Veteran-Owned Small Businesses to participate in the performance of the contract.

(3) If a subcontracting plan acceptable to the Contracting Officer is not negotiated within the time limits prescribed by the contracting activity and such failure arises out of causes within the control and with the fault or negligence of the offeror, the offeror shall be ineligible for an award. The Contracting Officer shall notify the Contractor in writing of the reasons for determining a subcontracting plan unacceptable early enough in the negotiation process to allow the Contractor to modify the plan within the time limits prescribed.

(4) Prior compliance of the offeror with other such subcontracting plans under previous contracts will be considered by the Contracting Officer in determining the responsibility of the offeror for award of the contract.

(5) It is the offeror's responsibility to develop a satisfactory subcontracting plan with respect to Small Business Concerns, Small Disadvantaged Business Concerns, Women-Owned Small Business Concerns, HubZone Small Business Concerns, Veteran-Owned Small Business Concerns, and Service Disabled Veteran-Owned Small Business Concerns that each such aspect of the offeror's plan will be judged independent of the other.

(6) The offeror will submit, as required by the Contracting Officer, subcontracting reports in accordance with the instructions thereon, and as further directed by the Contracting Officer. Subcontractors will also submit these reports to the Government's Contracting Officer or as otherwise directed, with a copy to the prime Contractor's designated small and disadvantaged business liaison.

d) Each plan must contain the following:

(1) Goals, expressed in terms of percentages of total planned subcontracting dollars, for the use of Small, Small Disadvantaged, Women-Owned, HUBZone, Veteran-Owned, and Service Disabled Veteran-Owned Small Business Concerns as subcontractors.

(2) A statement of total dollars planned to be subcontracted. A statement of total dollars to be subcontracted to each of the following type of small business concerns: Small, Small Disadvantaged, Women-Owned, HUBZone, Veteran-Owned, and Service Disabled Veteran-Owned Small Businesses.

(3) A description of the principal types of supplies and services to be subcontracted with an identification of which supplies and services are expected to be subcontracted to Small, Small Disadvantaged, Women-Owned, HUBZone, Veteran-Owned and/or Service Disabled Veteran-Owned Small Business Concerns.

(4) A description of the method used to develop the subcontracting goals.

(5) A description of the method used to identify potential sources for solicitation purposes.

(6) A statement as to whether or not indirect costs were included in establishing subcontracting goals. If they were, a description of the method used to determine the proportionate share of indirect costs to be incurred with Small, Small Disadvantaged, Women-Owned, HUBZone, Veteran-Owned, and Service Disabled Veteran-Owned Small Businesses.

(7) The name of the individual employed by the offeror who will administer the offeror's subcontracting program and a description of his/her duties.

(8) A description of the efforts the offeror will make to assure that Small, Small Disadvantaged, Women-Owned, HUBZone, Veteran-Owned, and Service Disabled Veteran-Owned Small Businesses have an equitable chance to compete for subcontracts.

(9) Assurances that the offeror will include in all subcontracts the contract clause "Utilization of Small Business Concerns." Assure that all subcontractors, other than small businesses, in excess of $500,000 adopt a plan similar to the plan agreed upon by the offeror.

(10) Assurances that the offeror (and any required subcontractors) will cooperate in studies or surveys as required and submit required reports (SF 294 and SF 295) to the Government.

List the types of records the offeror will maintain to demonstrate procedures that have been adopted to comply with the requirement and goals in the plan, including establishing source lists. Also, the offeror shall describe its efforts to locate Small, Small Disadvantaged, Women-Owned, HUBZone, Veteran-Owned, and Service Disabled Veteran-Owned Small Businesses and award subcontracts to them.

For additional information about each of the above elements required to be contained the subcontracting plan, see FAR Clause 52.219-9, Small Business Subcontracting Plan, and the Sample Subcontracting Plan which is provided as an attachment to this RFP in SECTION J.

(19) **HUBZone Small Business Concerns**

Small Business offerors located in underutilized business zones, called "HUBZones," will be evaluated in accordance with FAR Clause 52.219-4, NOTICE OF PRICE EVALUATION PREFERENCE FOR HUBZONE SMALL BUSINESS CONCERNS, which is incorporated by reference in ARTICLE I.3. of this solicitation. Qualified HUBZone firms are identified in the Small Business Administration website at http://www.sba.gov/hubzone.

(20) **Extent of Small Disadvantaged Business Participation**

In accordance with FAR Subpart 15.304(c)(4), the extent of participation of Small Disadvantaged Business (SDB) concerns in performance of the contract in the authorized NAICS Industry Subsectors shall be evaluated in unrestricted competitive acquisitions expected to exceed $500,000 ($1,000,000 for construction) subject to certain limitations (see FAR 19.1202-1 and 19.1202-2(b). The dollar amounts cited above include any option years/option quantities that may be included in this solicitation. The definition of a "small disadvantaged business" is cited in FAR 19.001.

The factor entitled “Extent of Small Disadvantaged Business Participation” as set forth under the Evaluation Criteria in Section M shall be used for evaluation purposes. Credit under this evaluation factor is not available to SDB concerns that receive a Price Evaluation Adjustment (PEA) under FAR 19.11. Therefore, an SDB will be evaluated on this factor only if that SDB concern waives the PEA. **Waiver of the price evaluation adjustment shall be clearly stated in the proposal.**

The Department of Commerce determines, on an annual basis, by Subsectors, as contained in the North American Industry Classification System (NAICS) codes, and region, if any, the authorized SDB procurement mechanisms and applicable factors (percentages). The NAICS codes can be found at: http://www.sba.gov/size

The Department of Commerce website for the annual determination is:
http://www.arnet.gov/References/sdbadjustments.htm

Offerors shall include with their offers, SDB targets, expressed as dollars and percentages of total contract value, in each of the applicable, authorized NAICS Industry Subsector(s). The applicable authorized NAICS Industry Subsector(s) for this project is (are) identified elsewhere in this RFP. A total target for SDB participation by the prime contractor, that includes any joint ventures and team members, shall be provided as well as a total target for SDB participation by subcontractors. In addition, offerors must provide information that describes their plans for

meeting the targets set forth in their proposal. **This information shall be provided in one clearly marked section of the Business Proposal, which shall describe the extent of participation of SDB concerns in the performance of the contract.**

If the evaluation factor in this solicitation includes an SDB evaluation factor or subfactor that considers the extent to which SDB concerns are specifically identified, the SDB concerns considered in the evaluation shall be listed in any resultant contract. Offerors should note that addressing the extent of small disadvantaged business participation **is not in any way intended to be a substitute** for submission of the subcontracting plan, if it is required by this solicitation. An example of the type of information that might be given (in addition to the narrative describing the plan for meeting the targets) follows:

EXAMPLE

Targets for SDB Participation - NAICS Industry Subsector 223

	SDB Percentage of Total Contract Value	**SDB Dollars**
Total Contract Value- $1,000,000	25%	$250,000
SDB Participation by Prime	10%	$100,000
(Includes joint venture partners and team arrangements)*		
SDB Participation by subcontractors	15%	$150,000

***NOTE:** FAR Subpart 9.6 defines “Contractor team arrangements” to include two or more companies forming a partnership or joint venture to act as a potential prime contractor, or a potential prime contractor who agrees with one or more companies to have them act as its subcontractors on a specific contract or acquisition program. For purposes of evaluation of the SDB participation factor, FAR 19.1202-4 requires that SDB joint ventures and teaming arrangements at the prime level be presented separately from SDB participation by subcontractors.

(21) **Reimbursement of Costs for Independent Research and Development Projects** (Commercial Organizations Only)

The primary purpose of the Public Health Service (PHS) is to support and advance independent research within the scientific community. This support is provided in the form of contracts and grants totaling approximately 7 billion dollars annually. PHS has established effective, time tested and well recognized and accepted procedures for stimulating and supporting this independent research by selecting from multitudes of proposals those research projects most worthy of support within the constraints of its appropriations. The reimbursement of independent research and development costs not incidental to product improvement, through the indirect cost mechanism, would circumvent this competitive process.

To ensure that all research and development projects receive similar and equal consideration, all offerors may compete for direct funding for independent research and development projects they consider worthy of support by submitting those projects to the appropriate Public Health Service grant and/or contract office for review. Since these projects may be submitted for direct funding, the successful offeror agrees that no costs for any independent research and development project, including applicable indirect costs, will be claimed under any contract resulting from this solicitation.

(22) **Salary Rate Limitation in Fiscal Year 2002** **

Offerors are advised that pursuant to P.L. 107-116, no NIH Fiscal Year 2002 (October 1, 2001 - September 30, 2002) funds may be used to pay the direct annual salary of an individual through any contract awarded as a result of this solicitation at a rate in excess of the Executive Schedule, Level I* (direct salary is exclusive of Overhead, Fringe Benefits and General and Administrative expenses, also referred to as "indirect cost" or "facilities and administrative (F&A) costs"). Direct salary has the same meaning as the term "institutional base salary." An individual's direct salary (or institutional base salary) is the annual compensation that the contractor pays for an individual's

appointment whether that individual's time is spent on research, teaching, patient care or other activities. Direct salary (or institutional base salary) excludes any income that an individual may be permitted to earn outside of duties to the contractor.

This does not preclude the offeror from absorbing that portion of an employee's annual salary (plus the dollar amount for fringe benefits and associated indirect costs) that exceeds a rate of the Executive Schedule, Level I*. The salary rate limitation set by P.L. 107-116 applies only to Fiscal Year 2002 funds, however, salary rate ceilings for subsequent years may be included in future DHHS appropriation acts. Multi-year contracts awarded pursuant to this solicitation may be subject to unilateral modifications by the Government if an individual's annual salary exceeds any salary rate ceiling established in future appropriations acts. The Executive Schedule, Level I* annual salary rate limit also applies to individuals proposed under subcontracts, however it does not apply to consultants. P.L. 107-116 states in pertinent part:

> "None of the funds appropriated in this Act for the National Institutes of Health, the Agency for Healthcare Research and Quality, and the Substance Abuse, and Mental Health Services Administration shall be used to pay the salary of an individual through a grant or extramural mechanism at a rate in excess of Executive Level I."

Information regarding the FY-2002 rate can be found at: http://www.opm.gov/oca/02tables/ex.pdf

It should be noted that a similar public law may be enacted in Fiscal Year 2003, at which time that public law will be incorporated into any resultant contract(s).

(23) **Institutional Responsibility Regarding Conflicting Interests of Investigators**

EACH INSTITUTION MUST:

(a) Maintain an appropriate written, enforced policy on conflict of interest that complies with 42 CFR Part 50 Subpart F and/or 45 CFR Part 94 as appropriate and inform each investigator of the Institution's policy, the Investigator's reporting responsibilities, and the applicable regulations. If the Institution carries out the NIH funded research through subgrantees, contractors or collaborators, the Institution must take reasonable steps to ensure that Investigators working for such entities comply with the regulations, either by requiring those investigators to comply with the Institution's policy or by requiring the entities to provide assurances to the Institution that will enable the Institution to comply with the regulations.

(b) Designate an Institutional official(s) to solicit and review financial disclosure statements from each Investigator who is planning to participate in NIH-funded research.

(c) Require that by the time an application/proposal is submitted to the NIH each investigator who is planning to participate in the NIH-funded research has submitted to the designated official(s) a listing of his/her known Significant Financial Interests (and those of his/her spouse and dependent children): (i) that would reasonably appear to be affected by the research for which the NIH funding is sought; and (ii) in entities whose financial interests would reasonably appear to be affected by the research. All financial disclosures must be updated during the period of the award, either on an annual basis or as new reportable Significant Financial Interests are obtained.

(d) Provide guidelines consistent with the regulations for the designated official(s) to identify conflicting interests and take such actions as necessary to ensure that such conflicting interests will be managed, reduced, or eliminated.

(e) Maintain records, identifiable to each award, of all financial disclosures and all actions taken by the institution with respect to each conflicting interest for: (1) in the case of grants, at least three years from the date of submission of the final expenditures report or, where applicable, from other dates specified in 45 CFR Part 74.53(b) and (2) in the case of contracts, 3 years after final payment or, where applicable, for the other time period specified in 48 CFR Part 4 Subpart 4.7, Contract Records Retention.

(f) Establish adequate enforcement mechanisms and provide for sanctions where appropriate.

(g) Certify, in each application/proposal for funding to which the regulations applies, that:

1) there is in effect at the Institution a written and enforced administrative process to identify and manage, reduce or eliminate conflicting interests with respect to all research projects for which funding is sought from the NIH;

2) prior to the Institution's expenditure of any funds under the award, the Institution will report to the awarding component the existence of a conflicting interest (but not the nature of the interest or other details) found by the Institution and assure that the interest has been managed, reduced or eliminated in accord with the regulations; and for any interest that the Institution identifies as conflicting subsequent to the expenditure of funds after award, the report will be made and the conflicting interest managed, reduced, or eliminated, at least on a temporary basis within sixty days of that identification;

3) the Institution agrees to make information available, upon request, to the awarding component regarding all conflicting interests identified by the Institution and how those interested have been managed, reduced, or eliminated to protect the research from bias; and

4) the Institution will otherwise comply with the regulations.

INSTITUTIONAL MANAGEMENT OF CONFLICTING INTERESTS

(a) The designated official(s) must: (1) review all financial disclosures; and (2) determine whether conflict of interest exists, and if so, determine what actions should be taken by the Institution to manage, reduce or eliminate such conflict of interest. **A conflict of interest exists when the designated official(s) reasonably determines that a Significant Financial Interest could directly and significantly affect the design, conduct, or reporting of the NIH-funded research**.

Examples of conditions or restrictions that might be imposed to manage actual or potential conflicts of interests include, but are not limited to:

(i) public disclosure of significant financial interests;
(ii) monitoring of research by independent reviewers;
(iii) modification of the research plan;
(iv) disqualification of the Investigator(s) from participation in all or a portion of the research funded by the awarding component;
(v) divestiture of significant financial interests; or
(vi) severance of relationships that create actual or potential conflicts of interests.

(b) An Institution may require the management of other conflicting financial interests in addition to those described in paragraph (a) of this section, as the Institution deems appropriate.

(24) **ROTC Access and Federal Military Recruiting on Campus**

Section 514 of the FY 1997 Appropriations Act prohibits NIH from providing contract funds to educational institutions that the Secretary of Defense determines have a policy or practice (regardless of when implemented) that either prohibits, or in effect prevents (1) the maintaining, establishing, or operation of a unit of the Senior Reserve Officer Training Corps at the covered education entity; or (2) a student at the covered educational entity from enrolling in a unit of the Senior Reserve Officer Training Corps at another institution of higher education.

Further, contract funds may not be provided to educational institutions that have a policy or practice that prohibits or prevents (1) entry to campuses, or access to students (who are 17 years of age or older) on campuses, for purposes of Federal military recruiting; or (2) access by military recruiters for purposes of Federal military recruiting to information pertaining to students (who are 17 years of age or older) enrolled at the covered educational entity.

(25) **Solicitation Provisions Incorporated by Reference**, FAR 52.252-1 (February 1998)

This Solicitation incorporates one or more solicitation provisions by reference, with the same force and effect as if they were given in full text. Upon request, the Contracting Officer will make their full text available. The offeror is cautioned that the listed provisions may include blocks that must be completed by the offeror and submitted with its

quotation or offer. In lieu of submitting the full text provisions, the offeror may identify the provision by paragraph identifier and provide the appropriate information with its quotation or offer. Also, the full text of a solicitation provision may be accessed electronically at this address: http://www.arnet.gov/far/.

FEDERAL ACQUISITION REGULATION (48 CFR CHAPTER 1):

a) Facilities Capital Cost of Money, FAR Clause 52.215-16, (October 1997).

b) Order of Precedence-Uniform Contract Format, FAR Clause 52.215-8, (October 1997).

c) Preaward On-Site Equal Opportunity Compliance Evaluation, (Over $10,000,000), FAR Clause 52.222-24, (February 1999).

b. **TECHNICAL PROPOSAL INSTRUCTIONS**

A detailed work plan must be submitted indicating how each aspect of the statement of work is to be accomplished. Your technical approach should be in as much detail as you consider necessary to fully explain your proposed technical approach or method. The technical proposal should reflect a clear understanding of the nature of the work being undertaken. The technical proposal must include information on how the project is to be organized, staffed, and managed. Information should be provided which will demonstrate your understanding and management of important events or tasks.

(1) **Technical Discussions**

The technical discussion included in the technical proposal should respond to the items set forth below:

a) **Statement of Work**

(1) Objectives

State the overall objectives and the specific accomplishments you hope to achieve. Indicate the rationale for your plan, and relation to comparable work in progress elsewhere. Review pertinent work already published which is relevant to this project and your proposed approach. This should support the scope of the project as you perceive it.

(2) Approach

Use as many subparagraphs, appropriately titled, as needed to clearly outline the general plan of work. Discuss phasing of research and, if appropriate, include experimental design and possible or probable outcome of approaches proposed.

(3) Methods

Describe in detail the methodologies you will use for the project, indicating your level of experience with each, areas of anticipated difficulties, and any unusual expenses you anticipate.

(4) Schedule

Provide a schedule for completion of the work and delivery of items specified in the statement of work. Performance or delivery schedules shall be indicated for phases or segments, as applicable, as well as for the overall program. Schedules shall be shown in terms of calendar months from the date of authorization to proceed or, where applicable, from the date of a stated event, as for example, receipt of a required approval by the Contracting Officer. Unless the request for proposal indicates that the stipulated schedules are mandatory, they shall be treated as desired or recommended schedules. In this event, proposals based upon the offeror's best alternative schedule, involving no overtime, extra shift or other premium, will be accepted for consideration.

b) **Personnel**

Describe the experience and qualifications of personnel who will be assigned for direct work on this program. Information is required which will show the composition of the task or work group, its general qualifications, and recent experience with similar equipment or programs. Special mention shall be made of direct technical supervisors and key technical personnel, and the approximate percentage of the total time each will be available for this program.

OFFERORS SHOULD ASSURE THAT THE PRINCIPAL INVESTIGATOR, AND ALL OTHER PERSONNEL PROPOSED, SHALL NOT BE COMMITTED ON FEDERAL GRANTS AND CONTRACTS FOR MORE THAN A TOTAL OF 100% OF THEIR TIME. IF THE SITUATION ARISES WHERE IT IS DETERMINED THAT A PROPOSED EMPLOYEE IS COMMITTED FOR MORE THAN 100% OF HIS OR HER TIME, THE GOVERNMENT WILL REQUIRE ACTION ON THE PART OF THE OFFEROR TO CORRECT THE TIME COMMITMENT.

(1) Principal Investigator/Project Director

List the name of the Principal Investigator/Project Director responsible for overall implementation of the contract and key contact for technical aspects of the project. Even though there may be co-investigators, identify the Principal Investigator/Project Director who will be responsible for the overall implementation of any awarded contract. Discuss the qualifications, experience, and accomplishments of the Principal Investigator/Project Director. State the estimated time to be spent on the project, his/her proposed duties, and the areas or phases for which he/she will be responsible.

(2) Other Investigators

List all other investigators/professional personnel who will be participating in the project. Discuss the qualifications, experience, and accomplishments. State the estimated time each will spend on the project, proposed duties on the project, and the areas or phases for which each will be responsible.

(3) Additional Personnel

List names, titles, and proposed duties of additional personnel, if any, who will be required for full-time employment, or on a subcontract or consultant basis. The technical areas, character, and extent of subcontract or consultant activity will be indicated and the anticipated sources will be specified and qualified. For all proposed personnel who are not currently members of the offeror's staff, a letter of commitment or other evidence of availability is required. A resume does not meet this requirement. Commitment letters for use of consultants and other personnel to be hired must include:

- The specific items or expertise they will provide.
- Their availability to the project and the amount of time anticipated.
- Willingness to act as a consultant.
- How rights to publications and patents will be handled.

(4) Resumes

Resumes of all key personnel are required. Each must indicate educational background, recent experience, specific or technical accomplishments, and a listing of relevant publications.

(2) **Technical Evaluation**

Proposals will be technically evaluated in accordance with the factors, weights, and order of relative importance as described in the Technical Evaluation Criteria (SEE SECTION M).

(3) **Additional Technical Proposal Information**

a) Proposals which merely offer to conduct a program in accordance with the requirements of the Government's scope of work will not be eligible for award. The offeror must submit an explanation of the proposed technical approach in conjunction with the tasks to be performed in achieving the project objectives.

b) The technical evaluation is conducted in accordance with the weighted technical evaluation criteria by an initial review panel. This evaluation produces a numerical score (points) which is based upon the information contained in the offeror's proposal only.

(4) **Other Considerations**

Record and discuss specific factors not included elsewhere which support your proposal. Using specifically titled subparagraphs, items may include:

a) Any agreements and/or arrangements with subcontractor(s). Provide as much detail as necessary to explain how the statement of work will be accomplished within this working relationship.

b) Unique arrangements, equipment, etc., which none or very few organizations are likely to have which is advantageous for effective implementation of this project.

c) Equipment and unusual operating procedures established to protect personnel from hazards associated with this project.

d) Other factors you feel are important and support your proposed research.

e) Recommendations for changing reporting requirements if such changes would be more compatible with the offeror's proposed schedules.

(5) **Information Technology Systems Security**

If this project involves Information Technology, the proposal must present a detailed outline of its proposed Information Technology systems security program which complies with the requirements of the Statement of Work, the Computer Security Act of 1987 Office of Management and Budget (OMB) Circular A-130, Appendix III, "Security of Federal Automated Information Systems," and the DHHS Automated Information Systems Security Program Handbook (Release 2.0, dated May, 1994). The proposal will also need to include similar information for any subcontract proposed.

NOTE: OMB A-130 is accessible via web site: http://www.whitehouse.gov/WH/EOP/OMB/html/circular.html

c. BUSINESS PROPOSAL INSTRUCTIONS

(1) Basic Cost/Price Information

The business proposal must contain sufficient information to allow the Government to perform a basic analysis of the proposed cost or price of the work. This information shall include the amounts of the basic elements of the proposed cost or price. These elements will include, as applicable, direct labor, fringe benefits, travel, materials, subcontracts, purchased parts, shipping, indirect costs and rate, fee, and profit.

(2) Proposal Cover Sheet

The following information shall be provided on the first page of your pricing proposal:

1. Solicitation, contract, and/or modification number;
2. Name and address of Offeror;
3. Name and telephone number of point of contact;
4. Name, address, and telephone number of Contract Administration Office, (if available);
5. Name, address, and telephone number of Audit Office (if available);
6. Proposed cost and/or price; profit or fee (as applicable); and total;
7. The following statement: By submitting this proposal, the offeror, if selected for discussions, grants the contracting officer or an authorized representative the right to examine, at any time before award, any of those books, records, documents, or other records directly pertinent to the information requested or submitted.
8. Date of submission; and
9. Name, title and signature of authorized representative.

This cover sheet information is for use by offerors to submit information to the Government when cost or pricing data are not required but information to help establish price reasonableness or cost realism is necessary. Such information is not considered cost or pricing data, and shall not be certified in accordance with FAR 15.406-2.

(3) Cost and Pricing Data

1. **General Instructions**

A. You must provide the following information on the first page of your pricing proposal:

(1) Solicitation, contract, and/or modification number;
(2) Name and address of offeror;
(3) Name and telephone number of point of contact;
(4) Name of contract administration office (if available);
(5) Type of contract action (that is, new contract, change order, price revision/redetermination, letter contract, unpriced order, or other);
(6) Proposed cost; profit or fee; and total;
(7) Whether you will require the use of Government property in the performance of the contract, and, if so, what property;
(8) Whether your organization is subject to cost accounting standards; whether your organization has submitted a CASB Disclosure Statement, and if it has been determined adequate; whether you have been notified that you are or may be in noncompliance with your Disclosure Statement or CAS, and, if yes, an explanation; whether any aspect of this proposal is inconsistent with your disclosed practices or applicable CAS, and, if so, an explanation; and whether the proposal is consistent with your established estimating and accounting principles and procedures and FAR Part 31, Cost Principles, and, if not, an explanation;
(9) The following statement: This proposal reflects our estimates and/or actual costs as of this date and conforms with the instructions in FAR 15.403-5(b)(1) and Table 15-2. By submitting this proposal, we grant the Contracting Officer and authorized representative(s) the right to examine, at any time before award, those records, which include books, documents, accounting procedures and practices, and other data, regardless of type and form or whether such supporting information is specifically referenced or included in the proposal as the basis for pricing, that will permit an adequate evaluation of the proposed price;

(10) Date of submission; and
(11) Name, title and signature of authorized representative.

B. In submitting your proposal, you must include an index, appropriately referenced, of all the cost or pricing data and information accompanying or identified in the proposal. In addition, you must annotate any future additions and/or revisions, up to the date of agreement on price, or an earlier date agreed upon by the parties, on a supplemental index.

C. As part of the specific information required, you must submit, with your proposal, cost or pricing data (that is, data that are verifiable and factual and otherwise as defined at FAR 15.401). You must clearly identify on your cover sheet that cost or pricing data are included as part of the proposal. In addition, you must submit with your proposal any information reasonably required to explain your estimating process, including--

(1) The judgmental factors applied and the mathematical or other methods used in the estimate, including those used in projecting from known data; and
(2) The nature and amount of any contingencies included in the proposed price.

D. You must show the relationship between contract line item prices and the total contract price. You must attach cost-element breakdowns for each proposed line item, using the appropriate format prescribed in the "Formats for Submission of Line Item Summaries" section of this table. You must furnish supporting breakdowns for each cost element, consistent with your cost accounting system.

E. When more than one contract line item is proposed, you must also provide summary total amounts covering all line items for each element of cost.

F. Whenever you have incurred costs for work performed before submission of a proposal, you must identify those costs in your cost/price proposal.

G. If you have reached an agreement with Government representatives on use of forward pricing rates/factors, identify the agreement, include a copy, and describe its nature.

H. As soon as practicable after final agreement on price or an earlier date agreed to by the parties, but before the award resulting from the proposal, you must, under the conditions stated in FAR 15.406-2, submit a Certificate of Current Cost or Pricing Data.

2. **Cost Elements**

Depending on your system, you must provide breakdowns for the following basic cost elements, as applicable:

A. **Materials and services**. Provide a consolidated priced summary of individual material quantities included in the various tasks, orders, or contract line items being proposed and the basis for pricing (vendor quotes, invoice prices, etc.). Include raw materials, parts, components, assemblies, and services to be produced or performed by others. For all items proposed, identify the item and show the source, quantity, and price. Conduct price analyses of all subcontractor proposals. Conduct cost analyses for all subcontracts when cost or pricing data are submitted by the subcontractor. Include these analyses as part of your own cost or pricing data submissions for subcontracts expected to exceed the appropriate threshold in FAR 15.403-4. Submit the subcontractor cost or pricing data as part of your own cost or pricing data as required in paragraph 2.A.(2) of this table. These requirements also apply to all subcontractors if required to submit cost or pricing data.

(1) *Adequate Price Competition*. Provide data showing the degree of competition and the basis for establishing the source and reasonableness of price for those acquisitions (such as subcontracts, purchase orders, material order, etc.) exceeding, or expected to exceed, the appropriate threshold set forth at FAR 15.403-4 priced on the basis of adequate price competition. For interorganizational transfers priced at other than the cost of comparable competitive commercial work of the division, subsidiary, or affiliate of the contractor, explain the pricing method (see FAR 31.205-26(e)).

(2) *All Other*. Obtain cost or pricing data from prospective sources for those acquisitions (such as subcontracts, purchase orders, material order, etc.) exceeding the threshold set forth in FAR 15.403-4

and not otherwise exempt, in accordance with FAR 15.403-1(b) (i.e., adequate price competition, commercial items, prices set by law or regulation or waiver). Also provide data showing the basis for establishing source and reasonableness of price. In addition, provide a summary of your cost analysis and a copy of cost or pricing data submitted by the prospective source in support of each subcontract, or purchase order that is the lower of either $10,000,000 or more, or both more than the pertinent cost or pricing data threshold and more than 10 percent of the prime contractor's proposed price. The Contracting Officer may require you to submit cost or pricing data in support of proposals in lower amounts. Subcontractor cost or pricing data must be accurate, complete and current as of the date of final price agreement, or an earlier date agreed upon by the parties, given on the prime contractor's Certificate of Current Cost or Pricing Data. The prime contractor is responsible for updating a prospective subcontractor's data. For standard commercial items fabricated by the offeror that are generally stocked in inventory, provide a separate cost breakdown, if priced based on cost. For interorganizational transfers priced at cost, provide a separate breakdown of cost elements. Analyze the cost or pricing data and submit the results of your analysis of the prospective source's proposal. When submission of a prospective source's cost or pricing data is required as described in this paragraph, it must be included along with your own cost or pricing data submission, as part of your own cost or pricing data. You must also submit any other cost or pricing data obtained from a subcontractor, either actually or by specific identification, along with the results of any analysis performed on that data.

B. **Direct Labor**. Provide a time-phased (e.g., monthly, quarterly, etc.) breakdown of labor hours, rates, and cost by appropriate category, and furnish bases for estimates.

C. **Indirect Costs**. Indicate how you have computed and applied your indirect costs, including cost breakdowns. Show trends and budgetary data to provide a basis for evaluating the reasonableness of proposed rates. Indicate the rates used and provide an appropriate explanation.

D. **Other Costs**. List all other costs not otherwise included in the categories described above (e.g., special tooling, travel, computer and consultant services, preservation, packaging and packing, spoilage and rework, and Federal excise tax on finished articles) and provide bases for pricing.

E. **Royalties**. If royalties exceed $1,500, you must provide the following information on a separate page for each separate royalty or license fee:

(1) Name and address of licensor.
(2) Date of license agreement.
(3) Patent numbers.
(4) Patent application serial numbers, or other basis on which the royalty is payable.
(5) Brief description (including any part or model numbers of each contract item or component on which the royalty is payable).
(6) Percentage or dollar rate of royalty per unit.
(7) Unit price of contract item.
(8) Number of units.
(9) Total dollar amount of royalties.
(10) If specifically requested by the Contracting Officer, a copy of the current license agreement and identification of applicable claims of specific patents (see FAR 27.204 and 31.205-37).

F. **Facilities Capital Cost of Money**. When you elect to claim facilities capital cost of money as an allowable cost, you must submit Form CASB-CMF and show the calculation of the proposed amount (see FAR 31.205-10).

3. **Formats for Submission of Line Item Summaries**

The detailed breakdown shall be in the format as shown on the form **Breakdown of Proposed Estimated Cost (plus fee) and Labor Hours** (SECTION J, List of Attachments). For each separate cost estimate, the offeror must furnish a breakdown by cost element as indicated above. In addition, summary total amounts shall be furnished. In the event the RFP cites specific line items, by number, a cost breakdown for each line item must be furnished.

To assist in the preparation of future cost estimates, the Projected Consumer Price Index may be accessed at: http://amb.nci.nih.gov/cpi.htm

4. There is a clear distinction between submitting cost or pricing data and merely making available books, records, and other documents without identification. The requirement for submission of cost or pricing data is met when all accurate cost or pricing data reasonably available to the offeror have been submitted, either actually or by specific identification, to the Contracting Officer or an authorized representative. As later information comes into your possession, it should be submitted promptly to the Contracting Officer in a manner that clearly shows how the information relates to the offeror's price proposal. The requirement for submission of cost or pricing data continues up to the time of agreement on price, or an earlier date agreed upon between the parties if applicable.

5. By submitting your proposal, you grant the Contracting Officer or an authorized representative the right to examine records that formed the basis for the pricing proposal. That examination can take place at any time before award. It may include those books, records, documents, and other types of factual information (regardless of form or whether the information is specifically referenced or included in the proposal as the basis for pricing) that will permit an adequate evaluation of the proposed price.

(4) Requirements for Cost or Pricing Data or Information Other than Cost and Pricing Data [FAR Clause 52.215-20 (October 1997)]

(a) Exceptions from cost or pricing data.

(1) In lieu of submitting cost or pricing data, offerors may submit a written request for exception by submitting the information described in the following subparagraphs. The Contracting Officer may require additional supporting information, but only to the extent necessary to determine whether an exception should be granted, and whether the price is fair and reasonable.

(i) Identification of the law or regulation establishing the price offered. If the price is controlled under law by periodic rulings, reviews, or similar actions of a governmental body, attach a copy of the controlling document, unless it was previously submitted to the contracting office.

(ii) Commercial item exception. For a commercial item exception, the offeror shall submit, at a minimum, information on prices at which the same item or similar items have previously been sold in the commercial market that is adequate for evaluating the reasonableness of the price for this acquisition. Such information may include--

(A) For catalog items, a copy of or identification of the catalog and its date, or the appropriate pages for the offered items, or a statement that the catalog is on file in the buying office to which the proposal is being submitted. Provide a copy or describe current discount policies and price lists (published or unpublished), e.g., wholesale, original equipment manufacturer, or reseller. Also explain the basis of each offered price and its relationship to the established catalog price, including how the proposed price relates to the price of recent sales in quantities similar to the proposed quantities;

(B) For market-priced items, the source and date or period of the market quotation or other basis for market price, the base amount, and applicable discounts. In addition, describe the nature of the market;

(C) For items included on an active Federal Supply Service Multiple Award Schedule contract, proof that an exception has been granted for the schedule item.

(2) The offeror grants the Contracting Officer or an authorized representative the right to examine, at any time before award, books, records, documents, or other directly pertinent records to verify any request for an exception under this provision, and the reasonableness of price. For items priced using catalog or market prices, or law or regulation, access does not extend to cost or profit information or other data relevant solely to the offeror's determination of the prices to be offered in the catalog or marketplace.

(b) Requirements for cost or pricing data. If the offeror is not granted an exception from the requirement to submit cost or pricing data, the following applies:

(1) The offeror shall prepare and submit cost or pricing data and supporting attachments in accordance with Table 15-2 of FAR 15.408.

(2) As soon as practicable after agreement on price, but before contract award (except for unpriced actions such as letter contracts), the offeror shall submit a Certificate of Current Cost or Pricing Data, as prescribed by FAR 15.406-2.

(End of provision)

Alternate I (October 1997). As prescribed in 15.408(l), substitute the following paragraph (b)(1) for paragraph (b)(1) of the basic provision:

(b) (1) The offeror shall submit cost or pricing data and supporting attachments in the following format:

The format specified in paragraph L.2.c.(4) Cost and Pricing Data, subparagraph 3. Formats for Submission of Line Item Summaries shall be used for the submission cost information. Submission of all other cost or pricing data shall be in accordance with Table 15-2 in FAR 15.408.

(5) Qualifications of the Offeror

You are requested to submit a summary of your "General Experience, Organizational Experience Related to this RFP, Performance History and Pertinent Contracts."

a) **General Experience**

General experience is defined as general background, experience and qualifications of the offeror. A discussion of proposed facilities which can be devoted to the project may be appropriate.

b) **Organizational Experience Related to the RFP**

Organizational experience is defined as the accomplishment of work, either past or on-going, which is comparable or related to the effort required by this RFP. This includes overall offeror or corporate experience, **but not** the experience and/or past performance of individuals who are proposed as personnel involved with the Statement of Work in this RFP.

Performance History

Performance history is defined as meeting contract objectives within **delivery** and **cost schedules** on efforts, either past or on-going, which is comparable or related to the effort required by this RFP.

c) **Pertinent Contracts**

Pertinent contracts is defined as a listing of each related contract completed within the last three years or currently in process. The listing should include: 1) the contract number; 2) contracting agency; 3) contract dollar value; 4) dates contract began and ended (or ends); 5) description of contract work; 6) explanation of relevance of work to this RFP; 7) actual delivery and cost performance versus delivery and cost agreed to in the contract(s). For award fee contracts, separately state in dollars the base fee and award fee available and the award fee actually received. The same type of organizational experience and past performance data should be submitted.

d) **Pertinent Grants**

List grants supported by the Government that involved similar or related work to that called for in this RFP. Include the grant number, involved agency, names of the grant specialist and the Science Administrator, identification of the work, and when performed.

You are cautioned that omission or an inadequate or inaccurate response to this very important RFP requirement could have a negative effect on the overall selection process. Experience and past performance are factors which are relevant to the ability of the offerors to perform and are considered in the source selection process.

(6) Other Administrative Data

a) **Property**

(1) It is DHHS policy that Contractors will provide all equipment and facilities necessary for performance of contracts. Exception may be granted to furnish Government-owned property, or to authorize purchase with contract funds, only when approved by the Contracting Officer. If the offeror is proposing that the Government provide any equipment, other than that specified under Government Furnished Property in the RFP, the proposal must include comprehensive justification which includes:

(a) An explanation that the item is for a special use essential to the direct performance of the contract and the item will be used exclusively for the purpose. Office equipment such as desks, office machines, etc., will not be provided under a contract except under very exceptional circumstances.

(b) No practical or economical alternative exists (e.g., rental, capital investment) that can be used to perform the work.

(2) The offeror shall identify Government-owned property in its possession and/or Contractor titled property acquired from Federal funds, which it proposes to use in the performance of the prospective contract.

(3) The management and control of any Government property shall be in accordance with DHHS Publication (OS) 686 entitled, "Contractors Guide for Control of Government Property (1990)," a copy of which will be provided upon request.

b) **Submission of Electronic Funds Transfer Information with Offer, FAR Clause 52.232-38** (MAY 1999)

The offeror shall provide, with its offer, the following information that is required to make payment by electronic funds transfer (EFT) under any contract that results from this solicitation. This submission satisfies the requirement to provide EFT information under paragraphs (b)(1) and (j) of the clause at 52.232-34, Payment by Electronic Funds Transfer--Other than Central Contractor Registration.

(1) The solicitation number (or other procurement identification number).
(2) The offeror's name and remittance address, as stated in the offer.
(3) The signature (manual or electronic, as appropriate), title, and telephone number of the offeror's official authorized to provide this information.
(4) The name, address, and 9-digit Routing Transit Number of the offeror's financial agent.
(5) The offeror's account number and the type of account (checking, savings, or lockbox).
(6) If applicable, the Fedwire Transfer System telegraphic abbreviation of the offeror's financial agent.
(7) If applicable, the offeror shall also provide the name, address, telegraphic abbreviation, and 9-digit Routing Transit Number of the correspondent financial institution receiving the wire transfer payment if the offeror's financial agent is not directly on-line to the Fedwire and, therefore, not the receiver of the wire transfer payment.

c) **Financial Capacity**

The offeror shall indicate if it has the necessary financial capacity, working capital, and other resources to perform the contract without assistance from any outside source. If not, indicate the amount required and the anticipated source.

d) **Incremental Funding**

An incrementally funded cost-reimbursement contract is a contract in which the total work effort is to be performed over a multiple year period and funds are allotted, as they become available, to cover discernible phases or increments of performance. The incremental funding technique allows for contracts to be awarded for periods in excess of one year even though the total estimated amount of funds expected to be obligated for the

contract are not available at the time of the contract award. If this requirement is specified elsewhere in this RFP, the offeror shall submit a cost proposal for each year. In addition, the following provisions are applicable:

HHSAR 352.232-75, Incremental Funding (January 2001)

(a) It is the Government's intention to negotiate and award a contract using the incremental funding concepts described in the clause entitled Limitation of Funds. Under the clause, which will be included in the resultant contract, initial funds will be obligated under the contract to cover the first year of performance. Additional funds are intended to be allotted to the contract by contract modification, up to and including the full estimated cost of the contract, to accomplish the entire project. While it is the Government's intention to progressively fund this contract over the entire period of performance up to and including the full estimated cost, the Government will not be obligated to reimburse the Contractor for costs incurred in excess of the periodic allotments, nor will the Contractor be obligated to perform in excess of the amount allotted.

(b) The Limitation of Funds clause to be included in the resultant contract shall supersede the Limitation of Cost clause found in the General Provisions.

(End of provision)

e) **Facilities Capital Cost of Money, FAR 52.215-16, (October 1997)**

(This is applicable if you are a commercial organization.)

(a) Facilities capital cost of money [(see FAR 15.408(h)] will be an allowable cost under the contemplated contract, if the criteria for allowability in subparagraph 31.205-10(a)(2) of the Federal Acquisition Regulation are met. One of the allowability criteria requires the prospective Contractor to propose facilities capital cost of money in its offer.

(b) If the prospective Contractor does not propose this cost, the resulting contract will include the clause Waiver of Facilities Capital Cost of Money.

(End of Provision)

If the offeror elects to claim this cost, the offeror shall specifically identify or propose it in the cost proposal for the contract by checking the appropriate box below.

[ ] The prospective Contractor has specifically identified or proposed facilities capital cost of money in its cost proposal and elects to claim this cost as an allowable cost under the contract. Submit Form CASB-CMF (see FAR 31.205-10).

[ ] The prospective Contractor has not specifically identified or proposed facilities capital cost of money in its proposal and elects not to claim it as an allowable cost under the contract.

(7) Subcontractors

If subcontractors are proposed, please include a commitment letter from the subcontractor detailing:

a) Willingness to perform as a subcontractor for specific duties (list duties).

b) What priority the work will be given and how it will relate to other work.

c) The amount of time and facilities available to this project.

d) Information on their cognizant field audit offices.

e) How rights to publications and patents are to be handled.

f) A complete cost proposal in the same format as the offeror's cost proposal.

Note: Organizations that plan to enter into a subcontract with an educational concern under a contract awarded under this RFP should refer to the following Web Site for a listing of clauses that are required to be incorporated in Research & Development (R&D) subcontracts with educational institutions:

http://ocm.od.nih.gov/contracts/rfps/FDP/PDPclausecover.htm

(8) Proposer's Annual Financial Report

All offerors included in the competitive range will be required to submit a copy of the organization's most recent annual financial report.

A copy of the organization's most recent annual report must be submitted as part of the business proposal.

(9) Representations and Certifications

One copy of the Representations and Certifications attached as Section K shall be completed and be signed by an official authorized to bind your organization. Additionally, a completed copy of the Representations and Certifications shall be submitted from any proposed subcontractor.

(10) Travel Costs/Travel Policy

a) **Travel Costs - Commercial**

Costs for lodging, meals, and incidental expenses incurred by Contractor personnel shall be considered to be reasonable and allowable to the extent they do not exceed on a daily basis the per diem rates set forth in the Federal Travel Regulations, General Services Administration (GSA). Therefore, if travel costs are applicable and proposed by offerors, please be advised that they shall be calculated using the per diem rate schedule as established by GSA. Reimbursement of travel costs under any contract awarded from this RFP shall be in accordance with FAR 31.205-46.

b) **Travel Policy**

All offerors included within the competitive range will be required to submit one copy of their written travel policy. A written travel policy for any proposed subcontractors shall also be submitted at that time. If an offeror (or any proposed subcontractor) does not have a written travel policy, the offeror shall so state.

One copy of the offeror's (and any proposed subcontractor's) written travel policy shall be included in the business proposal (original only). If an offeror (or any proposed subcontractor) does not have a written travel policy, the offeror shall so state.

SECTION M - EVALUATION FACTORS FOR AWARD

1. GENERAL

Selection of an offeror for contract award will be based on an evaluation of proposals against three factors. The factors in order of importance are: technical, cost/price and Small Disadvantaged Business (SDB) participation. Although technical factors are of paramount consideration in the award of the contract, cost/price and SDB participation are also important to the overall contract award decision. All evaluation factors other than cost or price, when combined, are significantly more important than cost or price.

The evaluation will be based on the demonstrated capabilities of the prospective Contractors in relation to the needs of the project as set forth in the RFP. The merits of each proposal will be evaluated carefully. Each proposal must document the feasibility of successful implementation of the requirements of the RFP. Offerors must submit information sufficient to evaluate their proposals based on the detailed criteria listed below.

2. EXTENT OF SMALL DISADVANTAGED BUSINESS PARTICIPATION

SDB participation will not be scored, but the Government's conclusions about overall commitment and realism of the offeror's SDB Participation targets will be used in determining the relative merits of the offeror's proposal and in selecting the offeror whose proposal is considered to offer the best value to the Government.

The extent of the offeror's Small Disadvantaged Business Participation Targets will be evaluated before determination of the competitive range. Evaluation of SDB participation will be assessed based on consideration of the information presented in the offeror's proposal. The Government is seeking to determine whether the offeror has demonstrated a commitment to use SDB concerns for the work that it intends to perform.

Offers will be evaluated on the following sub-factors:

(a) Extent of participation of SDB concerns in terms of the value of the total acquisition.
(b) The complexity and variety of the work SDB concerns are to perform. Greater emphasis will be given for arrangements where the SDB shall be performing work appropriate to the scientific objectives expressed in the statement of work.

3. TECHNICAL EVALUATION CRITERIA

The evaluation criteria are used by the technical evaluation committee when reviewing the technical proposals. The criteria below are listed in the order of relative importance with weights assigned for evaluation purposes.

CRITERA **WEIGHT**

A. TECHNICAL APPROACH (50 Points)

Soundness and practicality of the technical approach for executing the entire set of requirements specified in the Statement of Work. Adequate justification and substantiation for the recommended methods will be assessed as demonstration of the Offeror's understanding of the scope and purpose of this work, including discussion of potential difficulties that may arise in its performance. Adequacy, suitability, and availability of necessary patient populations at the participating clinical sites to ensure achievement of the scientific research agenda and enrollment in protocols, including women, minorities and children, as appropriate, must be documented in the proposal.
The evaluation will assess:

1. Research Agenda Quality (25 Points)

a. Quality of proposed research agenda for studies of herpesvirus infections and diseases. Adequacy of rationale and design for studies proposed. Adequacy of plans to identify and design studies on natural history and pathogenesis, viral diagnostics and assessment of development of resistance to antiviral therapies into the research agenda, as appropriate to assess important gaps in knowledge.

b. Quality of the proposed plan for incorporation of study recommendations of the expert panel and prioritization of studies.

2. Conduct of Multi-Center Trials (15 Points)

a. Adequacy of proposed plans for conducting clinical trials, including plans for recruitment of clinical sites and recruitment of patients. The patient recruitment plan should describe specific approaches for maximizing inclusion of minorities, both genders and children, when appropriate. Adequacy of plans for incentives to enhance site participation.

b. Adequacy of plans for organization of protocol teams and protocol development methods. Adequacy of the plan for soliciting, reviewing and prioritizing concepts for new clinical studies within the guidelines of an expert panel that makes recommendations on study direction annually.

c. Quality of sample protocol, manual of procedures, case report forms and data analysis plan.

3. Organizational/Administrative Framework (10 Points)

a. Adequacy of the administrative and organizational framework, with lines of authority and responsibility clearly delineated. Adequacy of the approach to ensure efficient and accurate protocol development processes, regulatory compliance of the clinical trials network and monitoring of ongoing clinical studies and sites.

b. Adequacy of the biostatistical expertise and data management systems. Quality of the central laboratory to support the proposed clinical trials in the development/characterization of methodology to assess infections, surrogate markers, or development of antiviral drug resistance.

B. PERSONNEL AND EXPERIENCE (35 Points)

1 . PI and C0-PI Qualifications (20 Points)

Adequacy of the professional qualifications and experience of the PI (and any co-PIs), the medical staff in the Central Unit, and the collaborating sites in multicenter trials of antiviral therapies. Demonstration of leadership and capability in the conduct of multi-center studies and in the clinical evaluation of antiviral therapies. Demonstrated expertise in the conduct of studies in special populations, e.g. pediatrics, immunocompromised patients. Demonstrated expertise in the conduct of clinical studies of herpesvirus infections.

2. Professional, Technical and Support staff (15 Points)

a. Adequacy of the qualifications and experience of the proposed professional statistical and data management staff in the planning and analysis of multi-center trials and trials for rare diseases in special patient populations.

b. Adequacy of the qualifications and experience of the proposed professional technical and support staff, including nurse coordinators, project management staff, regulatory staff and central laboratory staff.

C. ADMINISTRATION, FACILITIES AND RESOURCES (15 Points)

1. Adequacy of the plan for administration of the multi-site clinical trials group, including the time commitment of the proposed professional and support staff. Adequacy of organizational structure for support of multi-center clinical trials. Quality of the operational plan for support for protocol development, regulatory document management, clinical site monitoring and protocol specific instructional material (e.g., manual of procedures).

2. Adequacy of the facilities and equipment to carry out the studies proposed and management of the network of clinical sites.

3. Adequacy of Central Laboratory facilities to support multicenter clinical studies.